

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 403/14, 413/14, A61K 31/495	A1	(11) International Publication Number: WO 97/17338 (43) International Publication Date: 15 May 1997 (15.05.97)
(21) International Application Number: PCT/GB96/02682 (22) International Filing Date: 4 November 1996 (04.11.96) (30) Priority Data: 9523065.2 10 November 1995 (10.11.95) GB (71) Applicant (for all designated States except US): MERCK SHARP & DOHME LIMITED [GB/GB]; Hertford Road, Hoddesdon, Hertfordshire EN11 9BU (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): CHAMBERS, Mark, Stuart [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). HOBBS, Sarah, Christine [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). STREET, Leslie, Joseph [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). (74) Agent: THOMPSON, John; Merck & Co., Inc., European Patent Dept., Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: SUBSTITUTED 1-INDOLYLPROPYL-4-BENZYLPIPERAZINE DERIVATIVES		
(57) Abstract		
<p>A class of 1-[3-(1<i>H</i>-indol-3-yl)propyl]-4-benzylpiperazine derivatives, substituted at the 5-position of the indole nucleus by a 1,2,4-triazol-4-yl moiety, and on the methylene linkage of the benzyl moiety by a range of substituted alkyl groups, are selective agonists of 5-HT₁-like receptors, being potent agonists of the human 5-HT_{1D} receptor subtype whilst possessing at least a 10-fold selective affinity for the 5-HT_{1D} receptor subtype relative to the 5-HT_{1B} subtype; they are therefore useful in the treatment and/or prevention of clinical conditions, in particular migraine and associated disorders, for which a subtype-selective agonist of 5-HT_{1D} receptors is indicated, whilst eliciting fewer side-effects, notably adverse cardiovascular events, than those associated with non-subtype-selective 5-HT_{1D} receptor agonists.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

SUBSTITUTED 1-INDOLYLPROPYL-4-BENZYLPIPERAZINE
DERIVATIVES

The present invention relates to a class of substituted piperazine
5 derivatives which act on 5-hydroxytryptamine (5-HT) receptors, being
selective agonists of so-called "5-HT₁-like" receptors. They are therefore
useful in the treatment of clinical conditions for which a selective agonist
of these receptors is indicated.

It has been known for some time that 5-HT₁-like receptor agonists
10 which exhibit selective vasoconstrictor activity are of use in the treatment
of migraine (see, for example, A. Doenicke *et al.*, *The Lancet*, 1988, Vol. 1,
1309-11; and W. Feniuk and P.P.A. Humphrey, *Drug Development*
Research, 1992, 26, 235-240).

The human 5-HT₁-like or 5-HT_{1D} receptor has recently been shown
15 by molecular cloning techniques to exist in two distinct subtypes. These
subtypes have been termed 5-HT_{1D α} (or 5-HT_{1D-1}) and 5-HT_{1D β} (or
5-HT_{1D-2}), and their amino acid sequences are disclosed and claimed in
WO-A-91/17174.

The 5-HT_{1D α} receptor subtype in humans is believed to reside on
20 sensory terminals in the dura mater. Stimulation of the 5-HT_{1D α} subtype
inhibits the release of inflammatory neuropeptides which are thought to
contribute to the headache pain of migraine. The human 5-HT_{1D β} receptor
subtype, meanwhile, is located predominantly on the blood vessels and in
the brain, and hence may play a part in mediating constriction of cerebral
25 and coronary arteries, as well as CNS effects.

Administration of the prototypical 5-HT_{1D} agonist sumatriptan
(GR43175) to humans is known to give rise at therapeutic doses to certain
adverse cardiovascular events (see, for example, F. Willett *et al.*, *Br. Med.*
J., 1992, 304, 1415; J.P. Ottervanger *et al.*, *The Lancet*, 1993, 341, 861-2;
30 and D.N. Bateman, *The Lancet*, 1993, 341, 221-4). Since sumatriptan

barely discriminates between the human 5-HT_{1D α} and 5-HT_{1D β} receptor subtypes (cf. WO-A-91/17174, Table 1), and since it is the blood vessels with which the 5-HT_{1D β} subtype is most closely associated, it is believed that the cardiovascular side-effects observed with sumatriptan can be attributed to stimulation of the 5-HT_{1D β} receptor subtype. It is accordingly considered (cf. G.W. Rebeck *et al.*, *Proc. Natl. Acad. Sci. USA*, 1994, 91, 3666-9) that compounds which can interact selectively with the 5-HT_{1D α} receptor subtype, whilst having a less pronounced action at the 5-HT_{1D β} subtype, might be free from, or at any rate less prone to, the undesirable cardiovascular and other side-effects associated with non-subtype-selective 5-HT_{1D} receptor agonists, whilst at the same time maintaining a beneficial level of anti-migraine activity.

The compounds of the present invention, being selective 5-HT₁-like receptor agonists, are accordingly of benefit in the treatment of migraine and associated conditions, e.g. cluster headache, chronic paroxysmal hemicrania, headache associated with vascular disorders, tension headache and paediatric migraine. In particular, the compounds according to this invention are potent agonists of the human 5-HT_{1D α} receptor subtype. Moreover, the compounds in accordance with this invention have been found to possess at least a 10-fold selective affinity for the 5-HT_{1D α} receptor subtype relative to the 5-HT_{1D β} subtype, and they can therefore be expected to manifest fewer side-effects than those associated with non-subtype-selective 5-HT_{1D} receptor agonists.

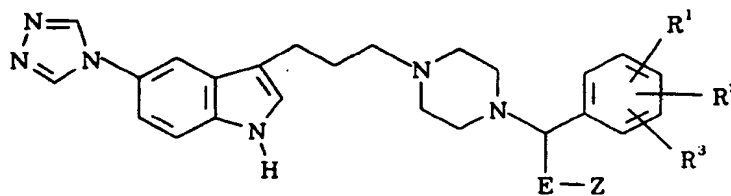
Several distinct classes of substituted five-membered heteroaromatic compounds are described in published European patent application 0497512, and published International patent applications 93/18029, 94/02477 and 94/03446. The compounds described therein are stated to be agonists of 5-HT₁-like receptors, and accordingly to be of particular use in the treatment of migraine and associated conditions. None of these publications, however, discloses nor even suggests the substituted piperazine derivatives provided by the present invention.

In EP-A-0548813 is described a series of alkoxy-pyridin-4-yl and alkoxy-pyrimidin-4-yl derivatives of indol-3-ylalkylpiperazines which are alleged to provide treatment of vascular or vascular-related headaches, including migraine. There is, however, no disclosure nor any suggestion in
5 EP-A-0548813 of replacing the alkoxy-pyridine or alkoxy-pyrimidine substituent with a substituted benzyl moiety; nor is there any suggestion therein that the range of substituents specified at the 5-position of the indole moiety might be replaced by a 1,2,4-triazol-4-yl ring.

Moreover, nowhere in the prior art mentioned above is there any
10 disclosure of a subtype-selective 5-HT_{1D} receptor agonist having a 5-HT_{1D α} receptor binding affinity (IC₅₀) below 50 nM and at least a 10-fold selective affinity for the 5-HT_{1D α} receptor subtype relative to the 5-HT_{1D β} subtype.

The compounds according to the present invention are subtype-selective 5-HT_{1D} receptor agonists having a human 5-HT_{1D α} receptor
15 binding affinity (IC₅₀) below 50 nM, typically below 10 nM and preferably below 1 nM; and at least a 10-fold selective affinity, typically at least a 50-fold selective affinity and preferably at least a 100-fold selective affinity, for the human 5-HT_{1D α} receptor subtype relative to the 5-HT_{1D β} subtype. Moreover, the compounds in accordance with this invention possess
20 interesting properties in terms of their efficacy and/or bioavailability.

The present invention provides a compound of formula I, or a salt or prodrug thereof:

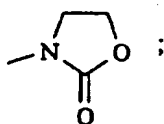


(I)

25

wherein

R^1 represents hydrogen, halogen, trifluoromethyl, C_{1-6} alkoxy or a group of formula (a):



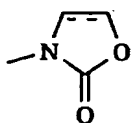
(a)

5

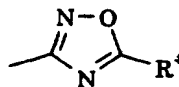
R^2 and R^3 independently represent hydrogen, halogen, trifluoromethyl or C_{1-6} alkoxy;

E represents a straight or branched alkylene chain containing from 1 to 4 carbon atoms; and

10 Z represents hydroxy, C_{1-6} alkoxy, aryl(C_{1-6})alkoxy, an imidazolyl or pyrrolidinyl group, or a group of formula (Za) or (Zb):



(Za)



(Zb)

15 in which the broken line represents an optional chemical bond; and
 R^4 represents C_{1-6} alkyl.

The compounds in accordance with the present invention are encompassed within the generic scope of co-pending International Patent Application No. PCT/GB95/01129, published as WO 95/32196 on 30
 20 November 1995. There is, however, no specific disclosure therein of compounds corresponding to those of formula I above wherein R^1 , R^2 , R^3 , E and Z are as defined above.

As used herein, the expression " C_{1-6} alkyl" includes methyl and ethyl groups, and straight-chained or branched propyl, butyl, pentyl and
 25 hexyl groups. Particular alkyl groups are methyl, ethyl, *n*-propyl,

isopropyl and *tert*-butyl. Derived expressions such as "C₁₋₆ alkoxy" are to be construed accordingly.

The term "aryl" as used herein includes phenyl and naphthyl.

A typical aryl(C₁₋₆)alkoxy group is benzyloxy.

5 The term "halogen" as used herein includes fluorine, chlorine, bromine and iodine, especially fluorine.

For use in medicine, the salts of the compounds of formula I will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their
10 pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, methanesulphonic acid,
15 fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid.

The present invention includes within its scope prodrugs of the compounds of formula I above. In general, such prodrugs will be functional derivatives of the compounds of formula I which are readily
20 convertible *in vivo* into the required compound of formula I. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in *Design of Prodrugs*, ed. H. Bundgaard, Elsevier, 1985.

The compounds according to the invention have at least one
25 asymmetric centre, and they may accordingly exist as enantiomers. Where the compounds according to the invention possess two or more asymmetric centres, they may additionally exist as diastereoisomers. It is to be understood that all such isomers and mixtures thereof in any proportion are encompassed within the scope of the present invention.

30 In the compounds of formula I above, the moiety R¹ suitably represents hydrogen, fluoro, trifluoromethyl, methoxy or a group of

formula (a) as defined above. Particular values of R^1 include hydrogen, fluoro and trifluoromethyl, especially hydrogen or fluoro.

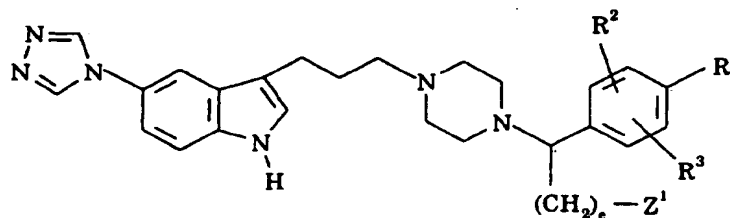
Suitably, R^2 and R^3 independently represent hydrogen, fluoro, trifluoromethyl or methoxy, in particular hydrogen or fluoro. Suitably,
 5 one or both of R^2 and R^3 represents hydrogen.

Suitably, R^4 represents methyl.

The alkylene chain E in the compounds of formula I above may be, for example, methylene, ethylene, 1-methylethylene, propylene, 2-methylpropylene or butylene. Suitably, E represents a methylene or
 10 ethylene linkage.

Particular values for the substituent Z include hydroxy, methoxy, benzyloxy, imidazol-1-yl, pyrrolidin-1-yl, oxazol-2-on-3-yl, oxazolidin-2-on-3-yl and 5-methyl-1,2,4-oxadiazol-3-yl.

A particular sub-class of compounds according to the invention is
 15 represented by the compounds of formula II, and salts and prodrugs thereof:



(II)

20 wherein R^1 , R^2 and R^3 are as defined above;

e is 1 or 2; and

Z^1 represents hydroxy, methoxy, benzyloxy, imidazol-1-yl, pyrrolidin-1-yl, oxazol-2-on-3-yl, oxazolidin-2-on-3-yl or 5-methyl-1,2,4-oxadiazol-3-yl.

25 Particular values of R^1 in relation to formula II above include hydrogen, fluoro and trifluoromethyl, especially hydrogen or fluoro.

In one embodiment of the compounds of formula II above, R² is hydrogen and R³ is other than hydrogen.

In another embodiment of the compounds of formula II above, R² and R³ are both hydrogen.

5 Specific compounds within the scope of the present invention include:

- 1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[2-(oxazol-2-on-3-yl)-1-phenylethyl]piperazine;
- 1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[2-(oxazolidin-2-on-3-yl)-1-phenylethyl]piperazine;
- 10 1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[1-(4-fluorophenyl)-2-(oxazolidin-2-on-3-yl)ethyl]piperazine;
- 1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-(3-hydroxy-1-phenylpropyl)piperazine;
- 15 1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[2-(imidazol-1-yl)-1-phenylethyl]piperazine;
- 1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[1-(4-fluorophenyl)-2-hydroxyethyl]piperazine;
- 1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[1-(4-fluorophenyl)-2-methoxyethyl]piperazine;
- 20 1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[3-(5-methyl-1,2,4-oxadiazol-3-yl)-1-phenylpropyl]piperazine;
- 1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[2-benzyloxy-1-(4-fluorophenyl)ethyl]piperazine;
- 25 1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[1-(4-fluorophenyl)-3-methoxypropyl]piperazine;
- 1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[1-(4-fluorophenyl)-2-(imidazol-1-yl)ethyl]piperazine;
- 1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[1-phenyl-2-(pyrrolidin-1-yl)ethyl]piperazine;
- 30

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[1-(4-fluorophenyl)-3-hydroxypropyl]piperazine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[3-(imidazol-1-yl)-1-phenylpropyl]piperazine;

5 and salts and prodrugs thereof.

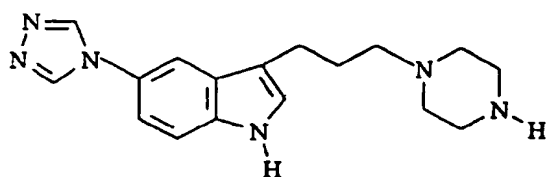
The invention also provides pharmaceutical compositions comprising one or more compounds of this invention in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules,
10 sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, auto-injector devices or suppositories; for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. For preparing solid compositions such as tablets, the principal active ingredient is mixed with
15 a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a
20 pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation
25 composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. Typical unit dosage forms contain from 1 to 100 mg, for example 1, 2, 5, 10, 25, 50 or 100 mg, of the active ingredient. The tablets or pills of the novel composition can be coated or otherwise compounded to
30 provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer

dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

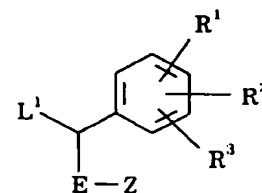
The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

In the treatment of migraine, a suitable dosage level is about 0.01 to 250 mg/kg per day, preferably about 0.05 to 100 mg/kg per day, and especially about 0.05 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day.

The compounds according to the invention may be prepared by a process which comprises reacting the compound of formula III with a compound of formula IV:



(III)



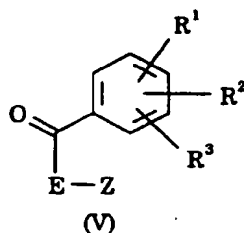
(IV)

wherein R^1 , R^2 , R^3 , E and Z are as defined above, and L^1 represents a suitable leaving group.

The leaving group L^1 is suitably a halogen atom, e.g. chlorine or bromine, or an alkylsulphonyloxy or arylsulphonyloxy group, e.g.
5 methanesulphonyloxy (mesyloxy) or *p*-toluenesulphonyloxy (tosyloxy).

The reaction between compounds III and IV is conveniently effected by stirring the reactants under basic conditions in a suitable solvent, for example triethylamine or potassium carbonate in *N,N*-dimethylformamide or isopropanol, typically in the presence of sodium iodide.

10 In another procedure, the compounds according to the invention may be prepared by a process which comprises reacting the compound of formula III as defined above with a compound of formula V:

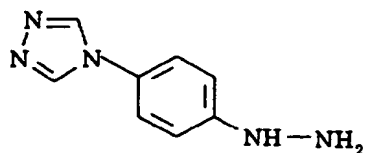


15

wherein R^1 , R^2 , R^3 , E and Z are as defined above; in the presence of a reducing agent.

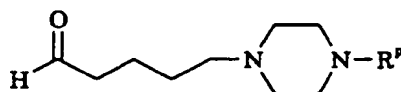
A suitable reducing agent for effecting this process is sodium cyanoborohydride, and the reaction is conveniently carried out in
20 methanol, typically in the presence of acetic acid, at room temperature.

The compound of formula III above may be prepared by a process which comprises reacting the compound of formula VI:



(VI)

with a compound of formula VII, or a carbonyl-protected form thereof:



(VII)

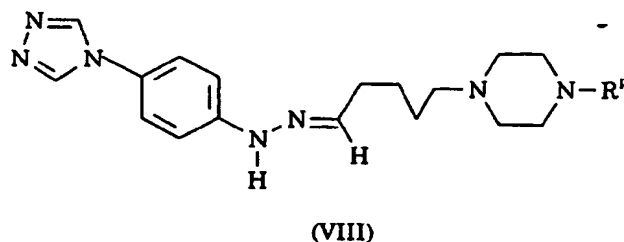
wherein R^p represents an amino-protecting group; with subsequent removal of the amino-protecting group R^p .

5 The reaction between compounds VI and VII, which is an example
10 of the well-known Fischer indole synthesis, is suitably carried out by
 heating the reagents together under mildly acidic conditions, e.g. 4%
 sulphuric acid at reflux.

 Suitable carbonyl-protected forms of the compounds of formula VII
 include the dimethyl acetal derivatives.

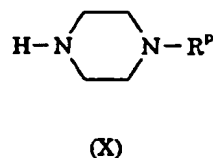
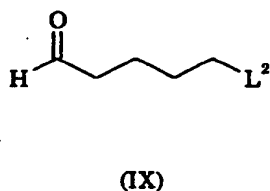
15 The protecting group R^p in the compounds of formula VII is suitably
 a carbamoyl moiety such as *tert*-butoxycarbonyl (BOC), which can
 conveniently be removed as necessary by treatment under mildly acidic
 conditions. Indeed, the acidic conditions of the Fischer indole synthesis
 reaction will generally suffice to remove the BOC group.

20 The Fischer reaction between compounds VI and VII may be carried
 out in a single step, or may proceed via an initial non-cyclising step at a
 lower temperature to give an intermediate of formula VIII:



wherein R^p is as defined above; followed by cyclisation using a suitable reagent, e.g. a polyphosphate ester.

- 5 The intermediates of formula VII, or carbonyl-protected forms thereof, may be prepared by reacting a compound of formula IX, or a carbonyl-protected form thereof, with a compound of formula X:



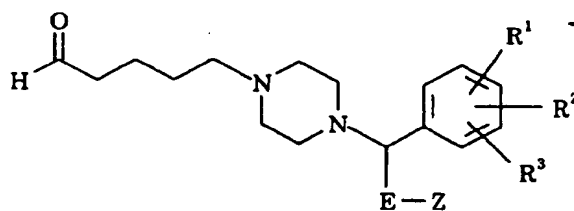
10

wherein R^p is as defined above, and L^2 represents a suitable leaving group.

The leaving group L^2 is suitably a halogen atom, e.g. chlorine or bromine.

- 15 Where L^2 represents a halogen atom, the reaction between compounds IX and X is conveniently effected by stirring the reactants under basic conditions in a suitable solvent, for example potassium carbonate in *N,N*-dimethylformamide, or triethylamine in tetrahydrofuran or acetonitrile.

- 20 The compounds according to the invention may alternatively be prepared by a process which comprises reacting the compound of formula VI as defined above with a compound of formula XI, or a carbonyl-protected form thereof:

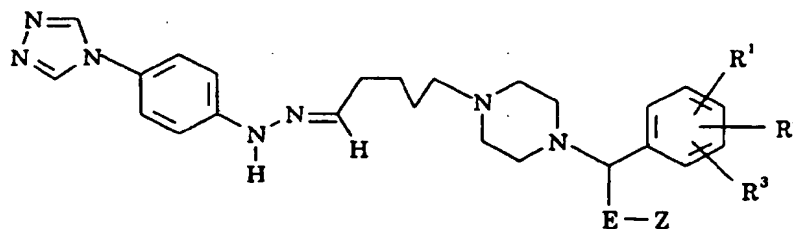


(XI)

wherein R^1 , R^2 , R^3 , E and Z are as defined above; under conditions analogous to those described above for the reaction between compounds VI and VII.

As for the compounds of formula VII, suitable carbonyl-protected forms of the compounds of formula XI include the dimethyl acetal derivatives.

As with that between compounds VI and VII, the Fischer reaction between compounds VI and XI may be carried out in a single step, or may proceed via an initial non-cyclising step at a lower temperature to give an intermediate of formula XII:



(XII)

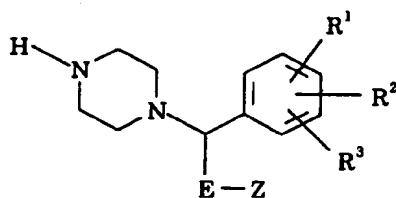
15

wherein R^1 , R^2 , R^3 , E and Z are as defined above; followed by cyclisation using a suitable reagent, e.g. a polyphosphate ester.

The intermediates of formula XI, or carbonyl-protected forms thereof, may be prepared by reacting a compound of formula IX as defined above, or a carbonyl-protected form thereof, with a compound of formula XIII:

20

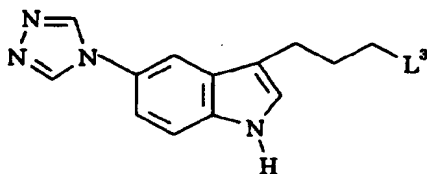
- 14 -



(XIII)

wherein R¹, R², R³, E and Z are as defined above; under conditions analogous to those described above for the reaction between compounds IX and X.

In an alternative procedure, the compounds of formula III above may be prepared by a process which comprises reacting a compound of formula X as defined above with a compound of formula XIV:



(XIV)

wherein L³ represents a suitable leaving group; followed by removal of the amino-protecting group R^p.

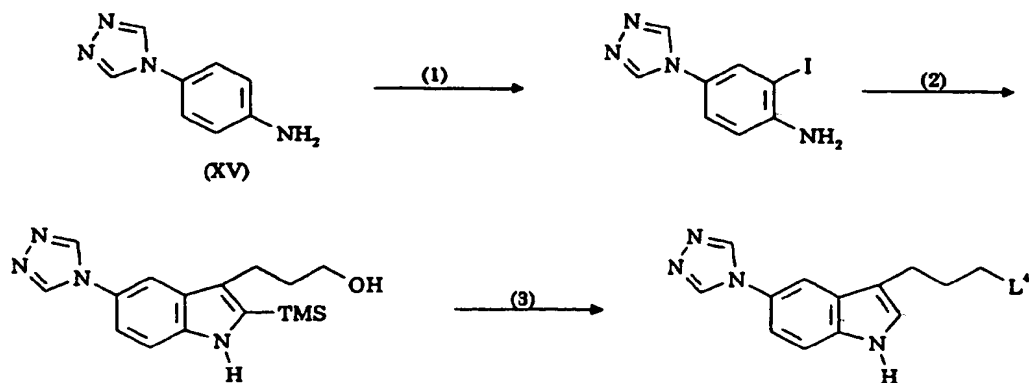
Similarly, the compounds of formula I as defined above may be prepared by a process which comprises reacting a compound of formula XIII as defined above with a compound of formula XIV as defined above.

The leaving group L³ is suitably an alkylsulphonyloxy or arylsulphonyloxy group, e.g. methanesulphonyloxy (mesyloxy) or *p*-toluenesulphonyloxy (tosyloxy).

Where L³ represents an alkylsulphonyloxy or arylsulphonyloxy group, the reaction between compound XIV and compound X or XIII is conveniently carried out in a suitable solvent such as 1,2-dimethoxyethane or isopropyl alcohol, typically in the presence of a base such as sodium

carbonate or potassium carbonate, optionally with the addition of sodium iodide.

In one representative approach, the compounds of formula XIV wherein L³ represents a mesyloxy or tosyloxy group may be prepared by the sequence of steps illustrated in the following reaction scheme (cf. Larock and Yum, *J. Am. Chem. Soc.*, 1991, 113, 6689):



wherein L⁴ represents mesyloxy or tosyloxy, and TMS is an abbreviation for trimethylsilyl.

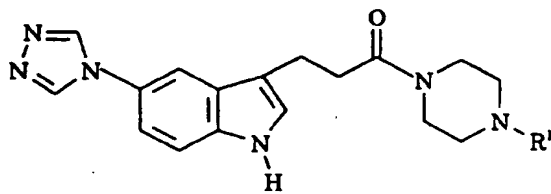
In Step 1 of the reaction scheme, the aniline derivative XV is treated with iodine monochloride, advantageously in methanol in the presence of a base such as calcium carbonate, in order to introduce an iodine atom *ortho* to the amine moiety. Step 2 involves a palladium-mediated coupling reaction with the protected acetylene derivative TMS-C≡C-(CH₂)₃-OH, typically using palladium acetate and triphenylphosphine in the presence of lithium chloride and sodium carbonate, suitably in *N,N*-dimethylformamide at an elevated temperature. This is followed in Step 3 by removal of the TMS moiety, ideally in refluxing methanolic hydrochloric acid; followed in turn by mesylation or tosylation, suitably by using mesyl chloride or tosyl chloride respectively in pyridine.

In another representative approach, the compounds of formula XIV wherein L³ represents a mesyloxy or tosyloxy group may be prepared by reacting 3,4-dihydro-2*H*-pyran with the compound of formula VI as defined

above or a salt thereof, under a variant of the Fischer reaction conditions as described above for the reaction between compounds VI and VII; followed by mesylation or tosylation of the 3-hydroxypropyl-indole derivative thereby obtained, typically by treatment with mesyl chloride or
5 tosyl chloride under standard conditions.

The Fischer reaction with 3,4-dihydro-2H-pyran is suitably brought about by heating the hydrazine derivative VI or an acid addition salt thereof, typically the hydrochloride salt, in an inert solvent such as dioxan, advantageously in the presence of a mineral acid such as hydrochloric acid
10 or a Lewis acid such as zinc chloride, at the reflux temperature of the solvent.

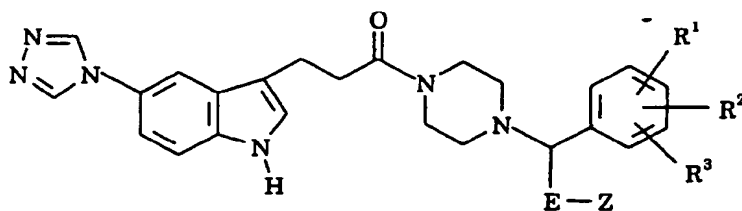
In a further procedure, the compounds of formula III above may be prepared by a process which comprises reducing a compound of formula
15 XVI:



(XVI)

wherein R^p is as defined above; with subsequent removal of the amino-protecting group R^p.

20 Similarly, the compounds according to the invention may be prepared by a process which comprises reducing a compound of formula XVII:

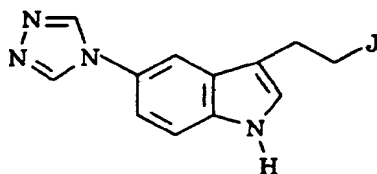


(XVII)

wherein R^1 , R^2 , R^3 , E and Z are as defined above.

The reduction of compound XVI or compound XVII is conveniently effected by treating the appropriate compound with a reducing agent such as lithium aluminium hydride in an appropriate solvent, e.g. diethyl ether or tetrahydrofuran, or mixtures thereof.

The compounds of formulae XVI and XVII above may suitably be prepared by reacting the appropriate compound of formula X or XIII with a compound of formula XVIII:



(XVIII)

wherein J represents a reactive carboxylate moiety.

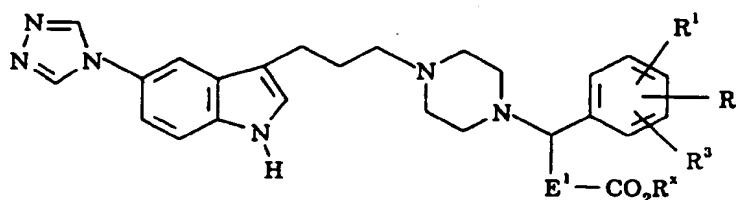
Suitable values for the reactive carboxylate moiety J include esters, for example C_{1-4} alkyl esters; acid anhydrides, for example mixed anhydrides with C_{1-4} alkanolic acids; acid halides, for example acid chlorides; and acylimidazoles.

By way of example, the intermediates of formula XVIII above wherein J is an acid chloride moiety may be prepared by treating the corresponding carboxylic acid derivative with thionyl chloride in toluene. Similarly, the intermediates of formula XVIII wherein J is an

acylimidazole moiety may be prepared by treating the corresponding carboxylic acid derivative with 1,1'-carbonyldiimidazole. Alternatively, the reactive carboxylate moiety J may be obtained by treating the corresponding compound wherein J is carboxy with

- 5 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 1-hydroxybenzotriazole hydrate, optionally in the presence of triethylamine; the resulting activated carboxylate intermediate may then suitably be reacted *in situ* with the required compound of formula X or XIII.

- 10 In a still further procedure, the compounds of formula I above wherein Z represents hydroxy may be prepared by a process which comprises reducing a compound of formula XIX:

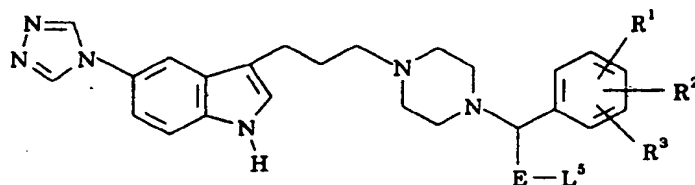


(XIX)

- 15 wherein E¹ represents a chemical bond or a straight or branched alkylene chain containing from 1 to 3 carbon atoms, R¹ represents C₁₋₆ alkyl, and R¹, R² and R³ are as defined above.

- The reduction of the ester functionality in compound XIX may conveniently be effected by treatment with a reducing agent such as
20 lithium aluminium hydride, typically in a solvent such as tetrahydrofuran.

In a yet further procedure, the compounds of formula I above wherein Z represents imidazol-1-yl, pyrrolidin-1-yl, oxazol-2-on-3-yl or oxazolidin-2-on-3-yl may be prepared by a process which comprises reacting a compound of formula XX with a compound of formula XXI:



(XX)



(XXI)

wherein Z^2 represents imidazol-1-yl, pyrrolidin-1-yl, oxazol-2-on-3-yl or oxazolidin-2-on-3-yl, L^5 represents a suitable leaving group, and R^1 , R^2 , R^3 and E are as defined above.

The leaving group L^5 suitably represents mesyloxy or tosyloxy.

Where Z^2 represents an oxazol-2-on-3-yl moiety, compound XXI is desirably treated with a strong base such as sodium hydride, in order to generate the anion thereof prior to reaction with compound XX. In this context, a suitable solvent is *N,N*-dimethylformamide, and the reaction is typically carried out at room temperature. Otherwise, the reaction between compounds XX and XXI can be effected in the absence of added base, and will conveniently be accomplished in tetrahydrofuran as solvent, at an elevated temperature under sealed tube conditions.

Where the leaving group L^5 is mesyloxy or tosyloxy, the intermediate of formula XX may conveniently be prepared by mesylation or tosylation respectively of the corresponding compound of formula I wherein Z is hydroxy. The latter compound may conveniently be prepared by reduction of the appropriate compound of formula XIX as described above.

The hydrazine derivative of formula VI above can be prepared by the method described in WO 94/03446, as also can the aniline derivative of formula XV.

Where they are not commercially available, the starting materials of formula IV, V, IX, X, XIII, XVIII, XIX and XXI may be prepared by methods analogous to those described in the accompanying Examples, or by standard procedures well known from the art.

It will be appreciated that any compound of formula I initially obtained from any one of the above processes may, where appropriate, subsequently be elaborated into a further compound of formula I using techniques known from the art. For example, a compound of formula I
5 wherein Z is hydroxy initially obtained may be converted into the corresponding compound wherein Z is amino by mesylation of the hydroxy group with mesyl chloride under standard conditions, followed by treatment with ammonia in methanol/tetrahydrofuran in a sealed tube at an elevated temperature; the resulting amino compound can then be
10 treated with 2-chloroethyl chloroformate to yield the respective chloroethyl carbamate derivative, with subsequent ring closure by treatment with sodium hydride to afford the desired compound of formula I wherein Z represents an oxazolidin-2-on-3-yl moiety.

Where the above-described processes for the preparation of the
15 compounds according to the invention give rise to mixtures of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. The novel compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The novel compounds
20 may, for example, be resolved into their component enantiomers by standard techniques such as preparative HPLC, or the formation of diastereomeric pairs by salt formation with an optically active acid, such as (-)-di-*p*-toluoyl-*d*-tartaric acid and/or (+)-di-*p*-toluoyl-*l*-tartaric acid, followed by fractional crystallization and regeneration of the free base.
25 The novel compounds may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the
30 molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic*

Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

5 The following Examples illustrate the preparation of compounds according to the invention.

 The compounds in accordance with the present invention potently and selectively bind to the 5-HT_{1D α} receptor subtype, inhibit forskolin-stimulated adenylyl cyclase activity, and stimulate [³⁵S]-GTP γ S binding to
10 membranes from clonal cell lines expressing human cloned receptors.

5-HT_{1D α} /5-HT_{1D β} Radioligand Binding

 Chinese hamster ovary (CHO) clonal cell lines expressing the
15 human 5-HT_{1D α} and 5-HT_{1D β} receptors were harvested in PBS and homogenised in ice cold 50 mM Tris-HCl (pH 7.7 at room temperature) with a Kinematica polytron and centrifuged at 48,000g at 4°C for 11 min. The pellet was then resuspended in 50 mM Tris-HCl followed by a 10 min incubation at 37°C. Finally the tissue was recentrifuged at 48,000g, 4°C
20 for 11 min and the pellet resuspended, in assay buffer (composition in mM: Tris-HCl 50, pargyline 0.01, CaCl₂ 4; ascorbate 0.1%; pH 7.7 at room temperature) to give the required volume immediately prior to use (0.2 mg protein/ml). Incubations were carried out for 30 min at 37°C in the presence of 0.02-150 nM [³H]-5-HT for saturation studies or 2-5 nM [³H]-5-
25 HT for displacement studies. The final assay volume was 1 ml. 5-HT (10 μ M) was used to define non-specific binding. The reaction was initiated by the addition of membrane and was terminated by rapid filtration through Whatman GF/B filters (presoaked in 0.3% PEI/ 0.5% Triton X) followed by 2 x 4 ml washings with 50 mM Tris-HCl. The radioactive filters were then
30 counted on a LKB beta or a Wallac beta plate counter. Binding parameters were determined by non-linear, least squares regression

analysis using an iterative curve fitting routine, from which IC_{50} (the molar concentration of compound necessary to inhibit binding by 50%) values could be calculated for each test compound. The IC_{50} values for binding to the 5-HT $_{1D\alpha}$ receptor subtype obtained for the compounds of the accompanying Examples were below 50 nM in each case. Furthermore, the compounds of the accompanying Examples were all found to possess a selective affinity for the 5-HT $_{1D\alpha}$ receptor subtype of at least 10-fold relative to the 5-HT $_{1D\beta}$ subtype.

10 5-HT $_{1D\alpha}$ /5-HT $_{1D\beta}$ Adenylyl Cyclase Assay

Studies were performed essentially as described in *J. Pharmacol. Exp. Ther.*, 1986, 238, 248. CHO clonal cell lines expressing the human cloned 5-HT $_{1D\alpha}$ and 5-HT $_{1D\beta}$ receptors were harvested in PBS and homogenised, using a motor driven teflon/glass homogeniser, in ice cold Tris HCl-EGTA buffer (composition in mM: Tris HCl 10, EGTA 1, pH 8.0 at room temperature) and incubated on ice for 30-60 min. The tissue was then centrifuged at 20,000g for 20 min at 4°C, the supernatant discarded and the pellet resuspended in Tris HCl-EDTA buffer (composition in mM: Tris HCl 50, EDTA 5, pH 7.6 at room temperature) just prior to assay. The adenylyl cyclase activity was determined by measuring the conversion of α -[^{33}P]-ATP to [^{33}P]-cyclic AMP. A 10 μ l aliquot of the membrane suspension was incubated, for 10-15 min, in a final volume of 50 μ l, at 30°C, with or without forskolin (10 μ M), in the presence or absence of test compound. The incubation buffer consisted of 50 mM Tris HCl (pH 7.6 at room temperature), 100 mM NaCl, 30 μ M GTP, 50 μ M cyclic AMP, 1 mM dithiothreitol, 1 mM ATP, 5 mM MgCl $_2$, 1 mM EGTA, 1 mM 3-isobutyl-1-methylxanthine, 3.5 mM creatinine phosphate, 0.2 mg/ml creatine phosphokinase, 0.5-1 μ Ci α -[^{33}P]-ATP and 1 nCi [3H]-cyclic AMP. The incubation was initiated by the addition of membrane, following a 5 min preincubation at 30°C, and was terminated by the addition of 100 μ l SDS

(composition in mM: sodium lauryl sulphate 2%, ATP 45, cyclic AMP 1.3, pH 7.5 at room temperature). The ATP and cyclic AMP were separated on a double column chromatography system (*Anal. Biochem.*, 1974, 58, 541). Functional parameters were determined using a least squares curve fitting programme ALLFIT (*Am. J. Physiol.*, 1978, 235, E97) from which E_{max} (maximal effect) and EC_{50} (the molar concentration of compound necessary to inhibit the maximal effect by 50%) values were obtained for each test compound. Of those compounds which were tested in this assay, the EC_{50} values for the 5-HT_{1D α} receptor obtained for the compounds of the accompanying Examples were below 500 nM in each case. Moreover, the compounds of the accompanying Examples which were tested were all found to possess at least a 10-fold selectivity for the 5-HT_{1D α} receptor subtype relative to the 5-HT_{1D β} subtype.

15 5-HT_{1D α} /5-HT_{1D β} GTP γ S Binding

Studies were performed essentially as described in *Br. J. Pharmacol.*, 1993, 109, 1120. CHO clonal cell lines expressing the human cloned 5-HT_{1D α} and 5-HT_{1D β} receptors were harvested in PBS and homogenised using a Kinematica polytron in ice cold 20 mM HEPES containing 10 mM EDTA, pH 7.4 at room temperature. The membranes were then centrifuged at 40,000g, 4°C for 15 min. The pellet was then resuspended in ice cold 20 mM HEPES containing 0.1 mM EDTA, pH 7.4 at room temperature and recentrifuged at 40,000g, 4°C for 15-25 minutes. The membranes were then resuspended in assay buffer (composition in mM: HEPES 20, NaCl 100, MgCl₂ 10, pargyline 0.01; ascorbate 0.1%; pH 7.4 at room temperature) at a concentration of 40 μ g protein/ml for the 5-HT_{1D α} receptor transfected cells and 40-50 μ g protein/ml for the 5-HT_{1D β} receptor transfected cells. The membrane suspension was then incubated, in a volume of 1 ml, with GDP (100 μ M for 5-HT_{1D α} receptor transfected cells, 30 μ M for the 5-HT_{1D β} receptor transfected cells) and test compound

at 30°C for 20 min and then transferred to ice for a further 15 min. [35S]-GTPγS was then added at a final concentration of 100 pM and the samples incubated for 30 min at 30°C. The reaction was initiated by the addition of membrane and was terminated by rapid filtration through
5 Whatman GF/B filters and washed with 5 ml water. The radioactive filters were then counted on a LKB beta counter. Functional parameters were determined by a non-linear, least squares regression analysis using an iterative curve fitting routine, from which E_{max} (maximal effect) and EC₅₀ (the molar concentration of compound necessary to inhibit the
10 maximal effect by 50%) values were obtained for each test compound. Of those compounds which were tested in this assay, the EC₅₀ values for the 5-HT_{1Dα} receptor obtained for the compounds of the accompanying Examples were below 500 nM in each case. Moreover, the compounds of the accompanying Examples which were tested were all found to possess
15 at least a 10-fold selectivity for the 5-HT_{1Dα} receptor subtype relative to the 5-HT_{1Dβ} subtype.

EXAMPLE 1

20 1-[3-(5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl)propyl]-4-[3-hydroxy-1-phenylpropyl]piperazine, 1.9 Hydrogen Oxalate

Intermediate 1: 4-(1,2,4-Triazol-4-yl)phenylhydrazine

Prepared as described in WO 94/03446, Example 1.

25

Intermediate 2: 1-(3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl)-4-(H)-piperazine, 3.5 Hydrogen Oxalate

30

1. 5-[4-(tert-Butyloxycarbonyl)piperazin-1-yl]pentanal dimethyl acetal

a) 5-Bromopentanal dimethyl acetal

To a solution of 5-bromovaleryl chloride (50g, 0.251mol) in anhydrous THF (500ml), at -78°C, was added lithium tri-*tert*-butoxyaluminumhydride (1.0M solution in tetrahydrofuran, 300ml; 0.30mol), keeping the temperature below -70°C. The solution was stirred at -78°C for 5h and then quenched by dropwise addition of 2M hydrochloric acid (350ml). The mixture was warmed to room temperature and stirred for 16h. Diethyl ether (500ml) was added, the aqueous phase separated and extracted further with ether (x 2). The combined extracts were washed with saturated Na₂CO₃ solution (x 1), water (x 1) and brine (x 2), dried (Na₂SO₄) and evaporated to give 5-bromovaleraldehyde (37.5g, 91%). A solution of 5-bromovaleraldehyde (37.5g, 0.227mol) in methanol (250ml) and concentrated sulphuric acid (0.5ml) was stirred at room temperature for 3h. The solvent was removed under vacuum and to the residue was added K₂CO₃ solution (50ml) and diethyl ether (500ml). The aqueous layer was separated and re-extracted with ether (x 2). The combined extracts were washed with water and brine, dried (Na₂SO₄) and evaporated. The crude product was chromatographed on silica gel eluting with diethyl ether/hexane (1:9) to give the title-acetal (27.5g, 57%). δ (250MHz, CDCl₃) 1.43-1.67 (4H, m, 2 of CH₂); 1.83-1.94 (2H, m, CH₂); 3.38 (6H, s, CH(OMe)₂); 3.42 (2H, t, J = 7Hz, CH₂Br), 4.37 (1H, t, J = 7Hz, CH(OMe)₂).

b) 5-[4-(*tert*-Butyloxycarbonyl)piperazin-1-yl]pentanal dimethyl acetal

A mixture of 5-bromovaleraldehyde dimethyl acetal (27.5g, 0.13mol), Na₂CO₃ (20.7g, 0.195mol), sodium iodide (19.5g, 0.13mol) and *tert*-butyl-1-piperazinecarboxylate (25.5g, 0.137mol), in dimethoxyethane (250ml), was heated at 100°C for 3h. Aluminium foil was wrapped around the vessel to exclude light. The mixture was cooled to room temperature and filtered. The filtrate was evaporated under reduced pressure and then EtOAc (50ml) added and the mixture filtered again to remove inorganic salts. The solvent was removed under vacuum and the residue

chromatographed on silica gel eluting with EtOAc to give the title-product (25.7g, 63%). δ (250MHz, CDCl_3) 1.29-1.71 (6H, m, 3 of CH_2); 1.46 (9H, s, $\text{OC}(\text{Me})_3$); 2.31-2.39 (6H, m, 3 of CH_2); 3.32 (6H, s, $\text{CH}(\text{OMe})_2$); 3.41-3.45 (4H, m, 2 of CH_2); 4.36 (1H, t, $J = 6\text{Hz}$, $\text{CH}(\text{OMe})_2$).

5

2. 1-(3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl)-4-(H)-piperazine. 3.5 Hydrogen Oxalate

A mixture of Intermediate 1 (5.0g, 28.6mmol) and 5-[4-(*tert*-butyloxycarbonyl)piperazin-1-yl]pentanal dimethylacetal (9.03g, 28.6mmol) in 4% sulphuric acid (150ml) was heated at reflux for 48h. The solution was cooled in an ice-bath, basified with solid K_2CO_3 and extracted with butan-1-ol (x 3). The solvent was removed under vacuum and azeotroped with hexane (x 2). The crude product was purified by chromatography on silica gel eluting with $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_3$ (30:8:1) to give the title-indole (3.9g, 44%). The 3.5 hydrogen oxalate salt was prepared using 200mg of free base: mp 90-92°C. (Found: C, 45.97; H, 4.76; N, 13.77. $\text{C}_{17}\text{H}_{22}\text{N}_6 \cdot 3.5(\text{C}_2\text{H}_2\text{O}_4)$ requires C, 46.08; H, 4.76; N, 13.43%); δ (360MHz, D_2O) 2.12-2.24 (2H, m, CH_2); 2.93 (2H, t, $J = 7\text{Hz}$, CH_2); 3.46-3.76 (8H, m, 4 of CH_2); 7.37 (1H, dd, $J = 1.9$ and 8.7Hz , Ar-H); 7.39 (1H, s, Ar-H); 7.66 (1H, d, $J = 8.7$, Ar-H); 7.82 (1H, d, $J = 1.9\text{Hz}$, Ar-H); 9.13 (2H, s, Triazole-H).

15
20

Step 1: 3-Bromo-3-phenylpropan-1-ol

To a solution of 3-phenylpropan-1-ol (5mL, 0.037mol) in CCl_4 (60mL) was added N-bromosuccinimide (6.5g, 0.037mol) and benzoyl peroxide (383mg of 70% technical grade, 1.1mmol). The mixture was heated at reflux for 3h, after which time the solution was cooled and filtered. The filtrate was removed *in vacuo* and the residue partitioned between Et_2O (100mL) and water (100mL). The organic layer was separated, dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel, eluting with petrol:EtOAc (2:1), to give the

25
30

bromide (3.7g, 47%) as a colourless oil. ¹H NMR (250MHz, CDCl₃) δ 2.13-2.26 (1H, m), 2.36-2.49 (1H, m), 3.40-3.53 (2H, m), 5.36 (1H, dd, J=8.9 and 5.9Hz), 7.27-7.49 (5H, m).

5 Step 2: 1-[3-(5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl)propyl]-4-[3-hydroxy-1-phenylpropyl]piperazine. 1.9 Hydrogen Oxalate

A solution of Intermediate 2 (250mg, 0.81mmol), 3-bromo-3-phenylpropan-1-ol (191mg, 0.89mmol) and K₂CO₃ (111mg, 0.81mmol) in DMF (7mL) was heated at 70°C for 2h. After this time more bromide
10 (38mg, 0.17mmol) was added and heating continued for a further 2h. The solvent was then removed *in vacuo* and the residue partitioned between CH₂Cl₂ (2x20mL) and water (20mL). The combined organic layers were dried (Na₂SO₄) and evaporated. The residue was chromatographed on silica gel, eluting with CH₂Cl₂:MeOH:NH₃ (95:5:1), to afford the title
15 piperazine (228mg, 64%) as a colourless oil. The hydrogen oxalate salt was prepared. mp. 153°C. C₂₆H₃₂N₆O. 1.9 (C₂H₂O₄) requires: C, 58.14; H, 5.86; N, 13.65%. Found: C, 57.79; H, 5.85; N, 13.92%. ¹H NMR (360MHz, d₆-DMSO) δ 1.79-1.87 (1H, m), 1.88-2.01 (2H, m), 2.04-2.15 (1H, m), 2.59-2.80 (4H, m), 2.82-3.39 (10H, m), 3.70-3.77 (1H, m), 7.24-7.36 (7H, m), 7.49
20 (1H, d, J=8.5Hz), 7.77 (1H, s), 8.99 (2H, s), 11.16 (1H, br s). MS (ES⁺) (445, M+1).

EXAMPLE 2

25 1-[3-(5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl)propyl]-4-[1-(4-fluorophenyl)-3-hydroxypropyl]piperazine. 1.5 Hydrogen Oxalate

Step 1: Ethyl 3-(4-fluorophenyl)prop-2-enoate

A solution of 4-fluorobenzaldehyde (8.6mL, 0.081mol) and
30 carboethoxymethylene triphenylphosphorane (34g, 0.097mol) in toluene (400mL) was heated at reflux for 3h. After this time the solvent was

removed *in vacuo* and the residue triturated in petrol:Et₂O (1:1). The mixture was filtered and the filtrate evaporated. The residue was chromatographed on silica gel, eluting with petrol:Et₂O (3:1), to afford the ester (14.4g, 92%) as a low-melting colourless solid. ¹H NMR (major isomer) (250MHz, CDCl₃) δ 1.34 (3H, t, J=7.0Hz), 4.26 (2H, q, J=7.0Hz), 6.36 (1H, d, J=16Hz), 7.07 (2H, dd, J_{HA-HB}=8.6Hz and J_{HA-F}=8.6Hz), 7.51 (2H, dd, J_{HB-HA}=8.6Hz and J_{HB-F}=5.3Hz), 7.65 (1H, d, J=16Hz).

Step 2: 3-Bromo-3-(4-fluorophenyl)propan-1-ol

10 A solution of the alkene (14.4g, 0.074mol) in EtOH (200mL) containing 10% Pd on C (1.0g) was hydrogenated at 40psi for 40 min. After this time the catalyst was removed by filtration and the filtrate evaporated. The residue was azeotroped with EtOH (50mL) and the crude ester (14g) isolated as a colourless oil and used directly without further purification.

15 To a stirred solution of the saturated ester (14g) in THF (300mL) at -10°C, under nitrogen, was added LiAlH₄ (78mL of a 1.0M solution in Et₂O, 78mmol) dropwise. After addition was complete the solution was stirred for a further 1h at 0°C. A solution of Na₂SO₄ (sat., 50mL) was added and the solid removed by filtration. The filtrate was removed *in vacuo* and the residue partitioned between Et₂O (200mL) and water (200mL). The organic layer was separated, dried (Na₂SO₄) and evaporated. The crude 3-(4-fluorophenyl)propan-1-ol (11g) was isolated as a colourless oil and used directly without further purification. To a solution of the alcohol (5g, prepared from above) in CCl₄ (100mL) was added N-bromosuccinimide (5.8g, 0.032mol) and benzoyl peroxide (331mg of 70% technical grade, 0.96mmol). The mixture was heated at reflux for 3h then the solution was cooled to room temperature and filtered. The filtrate was evaporated and the residue chromatographed on silica gel, eluting with petrol:Et₂O (2:1→1:1). The bromide (3.52g, 47%) was isolated as a pale yellow oil. ¹H NMR (250MHz, CDCl₃) δ 2.23-2.36 (1H, m), 2.41-

2.55 (1H, m), 3.67-3.90 (2H, m), 5.22 (1H, dd, $J=9.3$ and 5.7Hz), 7.04 (2H, dd, $J_{\text{HA-HB}}=8.6\text{Hz}$ and $J_{\text{HA-F}}=8.6\text{Hz}$), 7.39 (2H, dd, $J_{\text{HB-HA}}=8.6\text{Hz}$ and $J_{\text{HB-F}}=5.3\text{Hz}$).

5 Step 3: 1-[3-(5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl)propyl]-4-[1-(4-fluorophenyl)-3-hydroxypropyl]piperazine. 1.5 Hydrogen Oxalate

Prepared as described in Example 1, Step 2 using Intermediate 2 (381mg, 1.22mmol), 3-bromo-3-(4-fluorophenyl)propan-1-ol (369mg, 1.59mmol), K_2CO_3 (168mg, 1.22mmol) and DMF (9mL). The crude residue
10 was chromatographed on silica gel, eluting with $\text{CH}_2\text{Cl}_2:\text{MeOH}$ (95:5→90:10), to afford the title piperazine (411mg, 73%) as a pale yellow oil. The hydrogen oxalate salt was prepared. mp. 134°C . $\text{C}_{26}\text{H}_{31}\text{N}_6\text{OF} \cdot 1.5 (\text{C}_2\text{H}_2\text{O}_4)$. H_2O requires: C, 56.58; H, 5.89; N, 13.65%. Found C, 56.28; H, 6.05; N, 13.44%. ^1H NMR (250MHz, d_6 -DMSO) δ 1.70-2.13 (4H, m), 2.64-
15 3.39 (14H, m), 3.72-3.76 (1H, m), 7.15 (2H, dd, $J_{\text{HA-HB}}=8.9\text{Hz}$ and $J_{\text{HA-F}}=8.9\text{Hz}$), 7.22-7.30 (4H, m), 7.45 (1H, d, $J=8.6\text{Hz}$), 7.73 (1H, d, $J=2.0\text{Hz}$), 8.97 (2H, s), 11.15 (1H, br s). MS (ES^+) (463, $\text{M}+1$).

EXAMPLE 3

20

1-[3-(5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl)propyl]-4-[1-(4-fluorophenyl)-3-methoxypropyl]piperazine. 1.5 Hydrogen Oxalate

Step 1: 3-Bromo-3-(4-fluorophenyl)-1-methoxypropane

25 To a stirred solution of 3-(4-fluorophenyl)propan-1-ol (800mg, 5.2mmol) (see Example 2, Step 2) in DMF (20mL), under nitrogen, was added sodium hydride (250mg of a 60% dispersion in mineral oil, 6.24mmol). The mixture was stirred at 0°C for 20min then iodomethane (389 μL , 6.24mmol) was added. Stirring was continued for 30min then the
30 cooling bath was removed and the mixture stirred at room temperature for 1h. After this time more sodium hydride (125mg of a 60% dispersion in

mineral oil, 3.1mmol) followed by iodomethane (195 μ L, 3.1mmol) were added and the mixture stirred for a further 2h. The solvent was removed *in vacuo* and the residue partitioned between ether (2x50mL) and water (50mL). The combined organic layers were dried (Na₂SO₄) and
5 evaporated. The crude methyl ether (593mg), which was isolated as a colourless oil, was used in the subsequent reaction without further purification.

To a solution of the ether (590mg) (prepared as described above) in CCl₄ (20mL) was added N-bromosuccinimide (625mg, 3.51mmol) and
10 benzoyl peroxide (36mg of 70% technical grade, 0.1mmol). The mixture was heated at reflux for 1h then the solution was cooled to room temperature and filtered. The filtrate was removed *in vacuo* and the residue chromatographed on silica gel, eluting with petrol:Et₂O (8:1). The bromide (304mg, 35%) was isolated as a colourless oil. ¹H NMR (250MHz, CDCl₃) δ 2.22-2.36 (1H, m), 2.40-2.55 (1H, m), 3.33 (3H, s), 3.36-3.43 (1H,
15 m), 3.49-3.58 (1H, m), 5.17 (1H, dd, J=6.0 and 9.0Hz), 7.02 (2H, dd, J_{HA-HB}=8.6Hz and J_{HA-F}=8.6Hz), 7.38 (2H, dd, J_{HB-HA}=8.6Hz and J_{HB-F}=5.2Hz).

20 Step 2: 1-[3-(5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl)propyl]-4-[1-(4-fluorophenyl)-3-methoxypropyl]piperazine. 1.5 Hydrogen Oxalate

Prepared as described in Example 1, Step 2 using Intermediate 2 (200mg, 0.65mmol), 3-bromo-3-(4-fluorophenyl)-1-methoxypropane (237mg, 0.96mmol), K₂CO₃ (89mg, 0.65mmol) and DMF (10mL). The
25 crude residue was chromatographed on silica gel, eluting with CH₂Cl₂:MeOH:NH₃ (90:10:0 \rightarrow 90:10:1), to afford the title piperazine (163mg, 53%) as the free base. The hydrogen oxalate salt was prepared. mp. 166°C. C₂₇H₃₃N₆FO. 1.5(C₂H₂O₄). 1.2(H₂O) requires: C, 56.90; H, 6.11; N, 13.27%. Found: C, 57.23; H, 6.46; N, 13.07%. ¹H NMR (360MHz, d₆-
30 DMSO) δ 1.83-2.05 (3H, m), 2.13-2.22 (1H, m), 2.67-3.35 (17H, m), 3.70-3.74 (1H, m), 7.18 (2H, dd, J_{HA-HB}=8.8Hz and J_{HA-F}=8.8Hz), 7.28-7.32 (4H,

m), 7.49 (1H, d, J=8.5Hz), 7.77 (1H, d, J=1.9Hz), 8.99 (2H, s), 11.15 (1H, br s). MS (ES⁺) (477, M+1).

EXAMPLE 4

5

1-[3-(5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl)propyl]-4-[3-(5-methyl-1,2,4-oxadiazol-3-yl)-1-phenylpropyl]piperazine. 1.5 Hydrogen Oxalate

Intermediate 3: 3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propan-1-ol

10 A solution of Intermediate 1 (25g, 143mmol) in dioxan (250mL) was treated with dihydropyran (24g, 286mmol) followed by 1M hydrochloric acid (150mL) and heated at reflux for 18h. The mixture was evaporated then azeotroped with toluene. Inorganic solids were removed by treating the residue with a mixture of methanol and acetonitrile. The mother
15 liquors were chromatographed on silica gel, eluting with CH₂Cl₂:MeOH (9:1→4:1). The compound was recrystallised from acetonitrile to afford the title alcohol (10.24g, 30%) as a colourless solid. mp. 205-207°C. ¹H NMR (360MHz, d₆-DMSO) δ 1.81 (2H, quin, J=7.0Hz), 2.75 (2H, t, J=8.0Hz), 3.46 (2H, dt, J=6.0 and 5.0Hz), 4.43 (1H, t, J=5.0Hz), 7.26 (1H, d, J=2.0Hz), 7.29 (1H, dd, J=9.0 and 2.0Hz), 7.47 (1H, d, J=9.0Hz), 7.77 (1H,
20 d, J=2.0Hz), 9.01 (2H, s), 11.05 (1H, br s). MS (CI⁺) (243, M+1).

Step 1: 4-Bromo-4-phenylbutyronitrile

Prepared as described in Example 1, Step 1 using 4-
25 phenylbutyronitrile (5.2mL, 0.034mol), N-bromosuccinimide (6.65g, 0.037mol), benzoyl peroxide (352mg of 70% technical grade. 1.0mmol) and CCl₄ (60mL). The crude residue was chromatographed on silica gel, eluting with petrol:Et₂O (3:1). The bromide (5.62g, 74%) was isolated as a colourless oil. ¹H NMR (250MHz, CDCl₃) δ 2.36-2.64 (4H, m), 5.00-5.07
30 (1H, m), 7.29-7.43 (5H, m).

Step 2: 4-(4-*tert*-Butyloxycarbonylpiperazinyl)-4-phenylbutyronitrile

A solution of 1-(*tert*-butyloxycarbonyl)piperazine (1.73g, 9.3mmol), 4-bromo-4-phenylbutyronitrile (2.5g, 11mmol) and K₂CO₃ (1.4g, 10.2mmol) in DMF (40mL) was heated at 60°C for 4h. After this time the mixture
5 was cooled to room temperature, filtered and the filtrate evaporated. The residue was partitioned between EtOAc (100mL) and water (100mL). The organic layer was separated, dried (Na₂SO₄) and evaporated. The residue was chromatographed on silica gel, eluting with petrol:EtOAc (2:1). The piperazine (2.69g, 88%) was isolated as a pale yellow oil, which solidified
10 on standing in the fridge. ¹H NMR (250MHz, CDCl₃) δ 1.41 (9H, s), 1.94-2.46 (8H, m), 3.32-3.60 (5H, m), 7.15-7.42 (5H, m). MS (ES⁺) (330, M+1).

Step 3: 4-(4-*tert*-Butyloxycarbonylpiperazinyl)-4-phenylbutyl carboxamide

15 Oxime

To a solution of sodium methoxide in MeOH (183mg sodium in 25mL MeOH, 8.0mmol) was added hydroxylamine hydrochloride (0.55g, 8.0mmol). The mixture was stirred at room temperature for 15min then 4-(4-*tert*-butyloxycarbonylpiperazinyl)-4-phenylbutyronitrile (2.62g,
20 8.0mmol) was added. The mixture was heated at reflux for 16h then the solution was cooled to room temperature. The mixture was filtered, evaporated and the residue partitioned between EtOAc (60mL) and water (60mL). The organic layer was separated, dried (Na₂SO₄) and evaporated *in vacuo*. The residue was chromatographed on silica gel, eluting with
25 CH₂Cl₂:MeOH (90:10), to afford the amide oxime (934mg, 32%). ¹H NMR (360MHz, d₆-DMSO) δ 1.34 (9H, s), 1.73-2.30 (8H, m), 3.19-3.30 (4H, m), 3.39-3.45 (1H, m), 5.32 (2H, br s), 7.19-7.36 (5H, m), 8.70 (1H, s).

Step 4: 3-[3-[4-(tert-Butyloxycarbonyl)piperazin-1-yl]-3-phenyl]propyl-5-methyl-1,2,4-oxadiazole

To a solution of sodium methoxide in MeOH (59mg sodium in 20mL MeOH, 2.56mmol) at room temperature was added the amide oxime
5 (0.93g, 2.56mmol) followed by EtOAc (1.25mL). The mixture was heated at reflux for 2 days before more sodium (30mg, 1.3mmol) was added. Heating was continued for one further day before the addition of more sodium (30mg, 1.3mmol) followed by EtOAc (1.25mL). Heating at reflux was continued for 3 days before more sodium (30mg, 1.3mmol) and EtOAc
10 (1.25mL) were added. After heating for a further 2 days the solution was cooled to room temperature and the solvent evaporated. The residue was partitioned between EtOAc (20mL) and water (2x20mL). The organic phase was separated, dried (Na₂SO₄) and evaporated. The residue was chromatographed on silica gel, eluting with petrol:EtOAc (1:1→0:1). The
15 oxadiazole (783mg, 79%) was isolated as a colourless oil. ¹H NMR (360MHz, CDCl₃) δ 1.41 (9H, s), 2.08-2.42 (6H, m), 2.53 (3H, s), 2.59-2.70 (2H, m), 3.31-3.48 (5H, m), 7.20-7.38 (5H, m).

Step 5: 1-[3-(5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl)propyl]-4-[3-(5-methyl-1,2,4-oxadiazol-3-yl)-1-phenylpropyl]piperazine. 1.5 Hydrogen Oxalate

A solution of the oxadiazole (390mg, 1.0mmol) in CH₂Cl₂ (20mL) and trifluoroacetic acid (4mL) was stirred at room temperature overnight. The solvent was removed *in vacuo* and the residue partitioned between CH₂Cl₂ (2x20mL) and aqueous K₂CO₃ (10%, 20mL). The combined organic
25 layers were dried (Na₂SO₄) and evaporated. The crude amine (276mg) was used without further purification.

To a solution of Intermediate 3 (150mg, 0.62mmol) in THF (80mL), under nitrogen, at room temperature, was added triethylamine (188μL, 1.36mmol) and methanesulphonyl chloride (105μL, 1.36mmol). After
30 stirring for 1h more triethylamine (60μL, 0.43mmol) followed by methanesulphonyl chloride (30μL, 0.39mmol) were added. After stirring

for a further 30min more triethylamine (30 μ L, 0.21mmol) and methanesulphonyl chloride (15 μ L, 0.20mmol) were added. After a further 30min the solution was filtered and the filtrate evaporated *in vacuo*. The crude mesylate was used in the subsequent reaction without further purification.

To a solution of the crude mesylate in iso-propanol (25mL) was added the crude amine (276mg, prepared as described above), sodium iodide (93mg, 0.62mmol) and K₂CO₃ (297mg, 1.43mmol). The mixture was heated at reflux for 4h. The solution was then cooled and filtered and the filtrate evaporated. The residue was partitioned between CH₂Cl₂ (2x20mL) and water (20mL) and the combined organic layers dried (Na₂SO₄) and evaporated. The residue was chromatographed on silica gel, eluting with CH₂Cl₂:MeOH:NH₃ (95:5:0→90:10:0→90:10:1). The title piperazine (196mg, 62%) was isolated as a cream-coloured foam. The hydrogen oxalate salt was prepared. mp. 134°C. C₂₉H₃₄N₈O. 1.5(C₂H₂O₄). 0.5(H₂O) requires: C, 58.71; H, 5.85; N, 17.12%. Found: C, 58.65; H, 6.20; N, 16.82%. ¹H NMR (360MHz, d₆-DMSO) δ 1.90-2.10 (3H, m), 2.26-2.40 (1H, m), 2.42-3.30 (17H, m), 3.57-3.63 (1H, m), 7.25-7.40 (7H, m), 7.49 (1H, d, J=8.6Hz), 7.77 (1H, s), 8.99 (2H, s), 11.16 (1H, br s). MS (ES⁺) (511, M+1).

EXAMPLE 5

1-[3-(5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl)propyl]-4-[1-(4-fluorophenyl)-2-hydroxyethyl]piperazine. 1.1 Hydrogen Oxalate

Step 1: Methyl 2-bromo-2-(4-fluorophenyl)ethyl acetate

To a stirred solution of thionyl chloride (4.8mL, 0.066mol) in MeOH (100mL) at 0°C, under nitrogen, was added 4-fluorophenylacetic acid (5.1g, 0.033mol) portionwise. The cooling bath was removed and the solution stirred at room temperature for 2h. The solvents were removed *in vacuo*

and the crude methyl ester was isolated as a colourless oil. The ester was used in the subsequent reaction without further purification.

5 A solution of this ester, N-bromosuccinimide (6.17g, 0.035mol) and benzoyl peroxide (342mg of 70% technical grade, 0.99mol) in CCl₄ (60mL) was heated at reflux, under nitrogen, for 1h. After this time the solvent was evaporated and the residue partitioned between ether (100mL) and water (100mL). The organic layer was separated, dried (Na₂SO₄) and evaporated. The residue was chromatographed on silica gel, eluting with petrol:Et₂O (3:1), to afford the title bromide (7.33g, 90%) as a pale yellow
10 oil. ¹H NMR (250MHz, CDCl₃) δ 3.80 (3H, s), 5.34 (1H, s), 7.05 (2H, dd, J_{HA-HB}=8.7Hz and J_{HA-F}=8.7Hz), 7.53 (2H, dd, J_{HB-HA}=8.7Hz and J_{HB-F}=5.2Hz).

15 Step 2: Methyl 2-(4-fluorophenyl)-2-[1-(3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl)piperazin-4-yl]ethyl acetate

In the same was as that described in Example 1, Step 2, using Intermediate 2 (620mg, 2.0mmol), methyl 2-bromo-2-(4-fluorophenyl)ethyl acetate (543mg, 2.2mmol), K₂CO₃ (304mg, 2.2mmol) and DMF (15mL). The crude residue was chromatographed on silica gel, eluting with
20 CH₂Cl₂:MeOH (90:10) to afford the ester (0.85g, 82%) as a yellow foam. ¹H NMR (250MHz, CDCl₃) δ 1.87-2.03 (2H, m), 2.37-2.71 (10H, m), 2.79 (2H, t, J=7.4Hz), 3.68 (3H, s), 3.97 (1H, s), 7.03 (2H, dd, J_{HA-HB}=8.6Hz and J_{HA-F}=8.6Hz), 7.12-7.16 (2H, m), 7.38-7.49 (3H, m), 7.55 (1H, dd, J=1.7Hz), 8.44 (1H, br s), 8.46 (2H, s). MS (ES⁺) (477, M+1).

25

Step 3: 1-[3-(5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl)propyl]-4-[1-(4-fluorophenyl)-2-hydroxyethyl]piperazine. 1.1 Hydrogen Oxalate

To a solution of the methyl ester (785mg, 1.65mmol) in THF (30mL) at -10°C, was added LiAlH₄ (1.65mL of a 1.0M solution in ether,
30 1.65mmol) dropwise. The mixture was stirred at -10°C for 30min before more LiAlH₄ (0.33mL of a 1.0M solution in ether, 0.33mmol) was added.

After a further 30min Na_2SO_4 solution (sat., 2mL) was added dropwise and the cooling bath removed. The mixture was stirred for 30min then the undissolved solid was removed by filtration. The filtrate was evaporated and the residue chromatographed on silica gel, eluting with

5 $\text{CH}_2\text{Cl}_2:\text{MeOH}:\text{NH}_3$ (90:10:0→90:10:1). The alcohol (671mg, 91%) was isolated as a pale yellow foam. The hydrogen oxalate salt was prepared. mp. 110°C (dec.). $\text{C}_{25}\text{H}_{29}\text{N}_6\text{O}_7 \cdot 1.1(\text{C}_2\text{H}_2\text{O}_4) \cdot \text{H}_2\text{O}$ requires: C, 57.76; H, 5.92; N, 14.86%. Found: C, 58.06; H, 6.02; N, 14.54%. ^1H NMR (360MHz, d_6 -DMSO) δ 1.91-2.03 (2H, m), 2.37-3.20 (12H, m), 3.50-3.57 (1H, m), 3.63-

10 3.70 (1H, m), 3.72-3.77 (1H, m), 7.16 (2H, dd, $J_{\text{HA-HB}}=8.8\text{Hz}$ and $J_{\text{HA-F}}=8.8\text{Hz}$), 7.30-7.36 (4H, m), 7.49 (1H, d, $J=8.5\text{Hz}$), 7.77 (1H, s), 9.00 (2H, s), 11.16 (1H, br s). MS (ES^+) (449, $\text{M}+1$).

EXAMPLE 6

15

1-[3-(5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl)propyl]-4-[1-(4-fluorophenyl)-2-(imidazol-1-yl)ethyl]piperazine. 2.6 Hydrogen Oxalate

To a solution of 1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-4-[1-(4-fluorophenyl)-2-hydroxyethyl]piperazine (200mg, 0.45mmol) in THF

20 (10mL) at 0°C was added triethylamine (124 μL , 0.89mmol) followed by methanesulphonyl chloride (70 μL , 0.89mmol). The mixture was stirred at 0°C for 20min then the mixture filtered and the filtrate transferred to a sealed tube. Imidazole (608mg, 8.9mmol) was added and the mixture heated at 70°C for 1h. After this time the solvent was evaporated and the

25 residue partitioned between CH_2Cl_2 (50mL) and water (3x40mL). The organic phase was separated, dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel, eluting with $\text{CH}_2\text{Cl}_2:\text{MeOH}:\text{NH}_3$ (90:10:1). The imidazole (72mg, 32%) was isolated as a pale yellow foam. The hydrogen oxalate salt was prepared. mp. 93°C (dec.). $\text{C}_{28}\text{H}_{31}\text{N}_8\text{F} \cdot 2.6(\text{C}_2\text{H}_2\text{O}_4) \cdot 1.1(\text{H}_2\text{O})$ requires: C, 52.99; H, 5.14; N, 14.89%. Found: C, 52.76; H, 5.27; N, 15.07%. ^1H NMR (360MHz, d_6 -DMSO) δ 1.97-2.10 (2H,

30

m), 2.49-3.60 (14H, m), 5.70-5.75 (1H, m), 7.10 (1H, s), 7.22 (2H, dd, $J_{\text{HA-HB}}=8.8\text{Hz}$ and $J_{\text{HA-F}}=8.8\text{Hz}$), 7.30-7.36 (2H, m), 7.41-7.46 (3H, m), 7.50 (1H, d, $J=8.6\text{Hz}$), 7.80 (1H, s), 8.21 (1H, s), 9.01 (2H, s), 11.18 (1H, br s). MS (ES⁺) (499, M+1).

5

EXAMPLE 7

1-[3-(5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl)propyl]-4-[1-(4-fluorophenyl)-2-(oxazolidin-2-on-3-yl)ethyl]piperazine. 2.0 Hydrogen Oxalate

10

Step 1: 1-[3-(5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl)propyl]-4-[2-amino-1-(4-fluorophenyl)ethyl]piperazine

In the same way as that described in Example 6 using 1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-4-[1-(4-fluorophenyl)-2-

15 hydroxyethyl]piperazine (113mg, 0.25mmol), triethylamine (70 μ L, 0.50mmol), methanesulphonyl chloride (39 μ L, 0.50mmol) and THF (5mL). The crude mesylate was converted to the amine in the same manner as that used in Example 6, using ammonia (2.5mL of a 2M solution in MeOH, 5.0mmol). The amine (60mg, 53%) was isolated as a pale yellow foam. ¹H
20 NMR (250MHz, CDCl₃) δ 1.89-2.01 (2H, m), 2.27-2.85 (14H, m), 4.10 (1H, dd, $J=10.1$ and 3.8Hz), 7.00 (2H, dd, $J_{\text{HA-HB}}=8.7\text{Hz}$ and $J_{\text{HA-F}}=8.7\text{Hz}$), 7.13-7.16 (2H, m), 7.34 (2H, dd, $J_{\text{HB-HA}}=8.7\text{Hz}$ and $J_{\text{HB-F}}=5.5\text{Hz}$), 7.47 (1H, d, $J=8.6\text{Hz}$), 7.57 (1H, d, $J=1.9\text{Hz}$), 8.37 (1H, br s), 8.47 (2H, s). MS (ES⁺) (448, M+1).

25

Step 2: 1-[3-(5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl)propyl]-4-[2-(2-chloroethylcarbamoyl)-1-(4-fluorophenyl)ethyl]piperazine

To a solution of 1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-4-[2-amino-1-(4-fluorophenyl)ethyl]piperazine (60mg, 0.13mmol) in dioxane
30 (2mL) and water (1mL) was added NaOH (59 μ L of a 10%(w/v) aqueous solution, 0.15mmol), followed by 2-chloroethyl chloroformate (15 μ L).

0.14mmol). The mixture was stirred at room temperature for 45min then the solution was adjusted to pH 11 using aqueous NaOH. The mixture was stirred for a further 30min then the solvent removed *in vacuo*. The residue was partitioned between EtOAc (2x20mL) and water (20mL). The combined organic layers were dried (Na₂SO₄) and evaporated. The residue was chromatographed on silica gel, eluting with CH₂Cl₂:MeOH (90:10). The carbamate (47mg, 63%) was isolated as a colourless foam. ¹H NMR (250MHz, CDCl₃) δ 1.90-2.03 (2H, m), 2.37-2.92 (14H, m), 3.53-3.77 (2H, m), 4.20-4.31 (2H, m), 4.55-4.69 (1H, m), 5.77-5.88 (1H, m), 7.01 (2H, dd, J_{HA-HB}=8.7Hz and J_{HA-F}=8.7Hz), 7.13-7.28 (4H, m), 7.47 (1H, d, J=8.6Hz), 7.56 (1H, d, J=2.0Hz), 8.39 (1H, br s), 8.47 (2H, s). MS (ES⁺) (554/556, M+1).

Step 3: 1-[3-(5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl)propyl]-4-[1-(4-fluorophenyl)-2-(oxazolidin-2-on-3-yl)ethyl]piperazine 2.0 Hydrogen Oxalate

To a solution of the carbamate (47mg, 0.085mmol) in DMF (5mL) was added sodium hydride (3.4mg of a 60% dispersion in mineral oil, 0.085mmol), and the mixture stirred at room temperature for 45min. The mixture was then partitioned between CH₂Cl₂ (2x20mL) and water (20mL). The combined organic layers were dried (Na₂SO₄) and evaporated. The residue was chromatographed on silica gel, eluting with CH₂Cl₂:MeOH:NH₃ (90:10:0→90:10:1). The oxazolidinone (15mg, 34%) was isolated as a colourless gum. The hydrogen oxalate salt was prepared. mp. 128°C (dec.). C₂₈H₃₂N₇O₂F. 2.0(C₂H₂O₄). 0.7(H₂O) requires: C, 54.11; H, 5.31; N, 13.80%. Found: C, 54.12; H, 5.14; N, 13.73%. ¹H NMR (360MHz, d₆-DMSO) δ 1.98-2.10 (2H, m), 2.67-3.20 (12H, m), 3.21-3.30 (1H, m), 3.51-3.63 (1H, m), 4.19-4.30 (4H, m), 4.98-5.03 (1H, m), 7.20 (2H, dd, J_{HA-HB}=8.9Hz and J_{HA-F}=8.9Hz), 7.31-7.34 (2H, m), 7.40 (2H, dd, J_{HB-HA}=8.7Hz and J_{HB-F}=5.5Hz), 7.49 (1H, d, J=8.7Hz), 7.79 (1H, s), 9.01 (2H, s), 11.17 (1H, br s). MS (ES⁺) (518, M+1).

EXAMPLE 8

5 **1-[3-(5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl)propyl]-4-[1-(4-fluorophenyl)-2-methoxyethyl]piperazine 1.4 Hydrogen Oxalate**

Step 1: Methyl 2-(4-*tert*-butyloxycarbonylpiperazin-1-yl)-2-(4-fluorophenyl)ethyl acetate

To a solution of methyl 2-bromo-2-(4-fluorophenyl)ethyl acetate
10 (3.6g, 14.6mmol) in DMF (30mL) was added 1-(*tert*-butyloxycarbonyl)piperazine (2.71g, 14.6mmol) and K₂CO₃ (2.41g, 17.5mmol). The mixture was heated at 50°C for 45min then the solvent was evaporated. The residue was partitioned between EtOAc (150mL) and water (100mL). The organic layer was separated, dried (Na₂SO₄) and
15 evaporated. The residue was chromatographed on silica gel, eluting with hexane:EtOAc (4:1→2:1), to afford the title piperazine (4.65g, 91%) as a yellow oil. ¹H NMR (360MHz, d₆-DMSO) δ 1.37 (9H, s), 2.30-2.36 (4H, m), 3.26-3.31 (4H, m), 3.62 (3H, s), 4.22 (1H, s), 7.20 (2H, dd, J_{HA-HB}=8.9Hz and J_{HA-F}=8.9Hz), 7.42 (2H, dd, J_{HB-HA}=8.9Hz and J_{HB-F}=5.6Hz). MS (ES⁺)
20 (353, M+1).

Step 2: 2-[4-*tert*-Butyloxycarbonylpiperazin-1-yl]-2-[4-fluorophenyl]ethanol

To a solution of the ester (4.65g, 13.2mmol) in THF (100mL) at
25 -10°C was added LiAlH₄ (13.2mL of a 1.0M solution in ether, 13.2mmol) dropwise. After stirring at -10°C for 1h Na₂SO₄ solution (sat., 13.2mL) was added dropwise and the cooling bath removed. The mixture was stirred for 30min and the solid removed by filtration. The filtrate was evaporated and the residue chromatographed on silica gel, eluting with
30 EtOAc:petrol (1:1)→EtOAc:MeOH (99:1). The alcohol (4.17g, 97%) was isolated as a colourless oil. ¹H NMR (360MHz, d₆-DMSO) δ 1.36 (9H, s).

2.24-2.41 (4H, m), 3.20-3.30 (4H, m), 3.42-3.46 (1H, m), 3.61-3.70 (1H, m), 3.74-3.83 (1H, m), 4.52 (1H, t, $J=5.3\text{Hz}$), 7.13 (2H, dd, $J_{\text{HA-HB}}=8.7\text{Hz}$ and $J_{\text{HA-F}}=8.7\text{Hz}$), 7.31 (2H, dd, $J_{\text{HB-HA}}=8.7\text{Hz}$ and $J_{\text{HB-F}}=5.7\text{Hz}$). MS (ES^+) (325, $\text{M}+1$).

5

Step 3: 4-(tert-Butyloxycarbonyl)-1-[1-(4-fluorophenyl)-2-methoxyethyl]piperazine

To a solution of the alcohol in DMF (20mL) at 0°C , was added sodium hydride (204mg of a 60% dispersion in oil, 5.1mmol). After stirring at 0°C for 20min iodomethane (0.32mL, 5.1mmol) was added and the mixture stirred at 0°C for a further 30min. More sodium hydride (74mg of a 60% dispersion in oil, 1.9mmol) followed by iodomethane (0.12mL, 1.9mmol) were then added and the mixture stirred for 20min at 0°C followed by 30min at room temperature. The solvent was evaporated and the residue partitioned between EtOAc (2x50mL) and water (50mL). The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel, eluting with EtOAc:hexane (1:1) to afford the methyl ether (1.46g, 93%) as a colourless oil. ^1H NMR (360MHz, d_6 -DMSO) δ 1.36 (9H, s), 2.26-2.37 (4H, m), 3.19 (3H, s), 3.24-3.33 (4H, m), 3.59-3.71 (3H, m), 7.13 (2H, dd, $J_{\text{HA-HB}}=8.9\text{Hz}$ and $J_{\text{HA-F}}=8.9\text{Hz}$), 7.33 (2H, dd, $J_{\text{HB-HA}}=8.9\text{Hz}$ and $J_{\text{HB-F}}=5.7\text{Hz}$), MS (ES^+) (339, $\text{M}+1$).

Step 4: 1-[1-(4-Fluorophenyl)-2-methoxyethyl]piperazine

To a solution of 4-(tert-butyloxycarbonyl)-1-[1-(4-fluorophenyl)-2-methoxyethyl]piperazine (1.46g, 4.3mmol) in CH_2Cl_2 (40mL) was added trifluoroacetic acid (4mL), and the mixture stirred at room temperature for 3h. The solvent was evaporated and the residue azeotroped with toluene (2x20mL). The residue was partitioned between EtOAc (2x50mL) and Na_2CO_3 solution (sat., 50mL). The combined organic phases were dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel,

eluting with $\text{CH}_2\text{Cl}_2:\text{MeOH}:\text{NH}_3$ (90:10:1), to afford the piperazine (0.95g, 92%) as a pale yellow oil. ^1H NMR (360MHz, CDCl_3) δ 2.37-2.55 (4H, m), 2.86-2.89 (4H, m), 3.29 (3H, s), 3.45-3.48 (1H, m), 3.61 (1H, dd, $J=9.9$ and 5.2Hz), 3.71 (1H, dd, $J=9.9$ and 5.8Hz), 7.00 (2H, dd, $J_{\text{HA-HB}}=8.7\text{Hz}$ and $J_{\text{HA-F}}=8.7\text{Hz}$), 7.27 (2H, dd, $J_{\text{HB-HA}}=8.7\text{Hz}$ and $J_{\text{HB-F}}=5.6\text{Hz}$). MS (ES^+) (239, $\text{M}+1$).

Step 5: 1-[3-(5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl)propyl]-4-[1-(4-fluorophenyl)-2-methoxyethyl]piperazine. 1.4 Hydrogen Oxalate

10 To a solution of Intermediate 3 (125mg, 0.52mmol) in THF (80mL) was added triethylamine (144 μL , 1.03mmol) and methanesulphonyl chloride (80 μL , 1.03mmol). After stirring at room temperature for 2h more triethylamine (72 μL , 0.51mmol) followed by methanesulphonyl chloride (40 μL , 0.51mmol) were added and the mixture stirred for a further 1h.

15 After this time the mixture was filtered and the filtrate evaporated *in vacuo*. The crude mesylate was used in the subsequent reaction without further purification.

To a suspension of the crude mesylate (prepared above) in iso-propanol (20mL) was added K_2CO_3 (214mg, 1.55mmol), sodium iodide (77mg, 0.52mmol) and a solution of 1-[1-(4-fluorophenyl)-2-methoxyethyl]piperazine (615mg, 2.6mmol) in iso-propanol (5mL). The mixture was heated at reflux, in the dark, for 3h. The solution was allowed to cool to room temperature and the precipitate removed by filtration. The filtrate was evaporated and the residue partitioned

20 between CH_2Cl_2 (2x50mL) and water (50mL). The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel, eluting with $\text{CH}_2\text{Cl}_2:\text{MeOH}$ (9:1 \rightarrow 4:1), to give the title indole (232mg, 97%) as a pale yellow foam. The hydrogen oxalate salt was prepared. mp. 100°C (dec.). $\text{C}_{26}\text{H}_{31}\text{N}_6\text{OF} \cdot 1.4(\text{C}_2\text{H}_2\text{O}_4) \cdot 1.5(\text{H}_2\text{O})$ requires: C, 56.19; H, 6.03; N, 13.65%. Found: C, 56.56; H, 6.35; N, 13.34%. ^1H NMR (360MHz, d_6 -DMSO) δ 1.91-2.03 (2H, m), 2.50-3.23

30

(15H, m), 3.58-3.62 (1H, m), 3.67-3.71 (2H, m), 7.16 (2H, dd, $J_{\text{HA-HB}}=8.9\text{Hz}$ and $J_{\text{HA-F}}=8.9\text{Hz}$), 7.30-7.37 (4H, m), 7.49 (2H, d, $J=8.5\text{Hz}$), 7.78 (1H, d, $J=1.9\text{Hz}$), 9.00 (2H, s), 11.17 (1H, br s). MS (ES⁺) (463, M+1).

5

EXAMPLE 9**1-[3-(5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl)propyl]-4-[2-benzyloxy-1-(4-fluorophenyl)ethyl]piperazine. 1.5 Hydrogen Oxalate****10 Step 1: 1-[2-Benzyloxy-1-(4-fluorophenyl)ethyl]-4-(tert-butylloxycarbonyl)piperazine**

In the same way as that described in Example 8, Step 3 using 2-[4-*tert*-butylloxycarbonylpiperazin-1-yl]-2-[4-fluorophenyl]ethan-1-ol (1.5g, 4.6mmol), sodium hydride (204mg of a 60% dispersion in oil, 5.1mmol) and
15 benzyl bromide (0.61mL, 5.1mmol). After stirring at room temperature for 30min more sodium hydride (37mg of a 60% dispersion in oil, 0.92mmol) followed by benzyl bromide (0.11mL, 0.92mmol) was added. The residue was chromatographed on silica gel, eluting with EtOAc:hexane (1:4→1:2), to afford the benzyl ether (1.58g, 82%) as a colourless oil. ¹H NMR
20 (250MHz, CDCl₃) δ 1.43 (9H, s), 2.30-2.55 (4H, m), 3.33-3.45 (4H, m), 3.51-3.60 (1H, m), 3.61-3.71 (1H, m), 3.73-3.85 (1H, m), 4.48 (2H, s), 6.96-7.04 (2H, m), 7.20-7.40 (7H, m). MS (ES⁺) (415, M+1).

Step 2: 1-[2-Benzyloxy-1-(4-fluorophenyl)ethyl]piperazine

25 In the same way as that described in Example 8, Step 4 using 1-[2-benzyloxy-1-(4-fluorophenyl)ethyl]-4-(*tert*-butylloxycarbonyl)piperazine (1.58g, 3.8mmol), trifluoroacetic acid (5mL) and CH₂Cl₂ (50mL). The piperazine (1.11g, 92%) was isolated as a colourless oil. ¹H NMR
(250MHz, CDCl₃) δ 2.36-2.57 (4H, m), 2.84-2.89 (4H, m), 3.49-3.54 (1H, m),
30 3.65 (1H, dd, $J=9.9$ and 5.4Hz), 3.79 (1H, dd, $J=9.9$ and 5.8Hz), 4.47 (2H,

s), 6.99 (1H, dd, $J_{\text{HA-HB}}=8.7\text{Hz}$ and $J_{\text{HA-F}}=8.7\text{Hz}$), 7.20-7.35 (7H, m). MS (ES⁺) (315, M+1).

5 Step 3: 1-[3-(5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl)propyl]-4-[2-benzyloxy-1-(4-fluorophenyl)ethyl]piperazine. 1.5 Hydrogen Oxalate

In the same way as that described in Example 8, Step 5, using Intermediate 3 (100mg, 0.41mmol), triethylamine (172 μ L; 1.24mmol), methanesulphonyl chloride (96 μ L, 1.24mmol) and THF (70mL). After stirring at room temperature for 3h more triethylamine (57 μ L, 0.41mmol) followed by methanesulphonyl chloride (32 μ L, 0.41mmol) were added. After stirring at room temperature for a further 90min the resultant crude mesylate was obtained and used crude in the subsequent reaction.

The crude mesylate (prepared above), 1-[2-benzyloxy-1-(4-fluorophenyl)ethyl]piperazine (649mg, 2.07mmol), K₂CO₃ (171mg, 1.24mmol), sodium iodide (62mg) and iso-propanol (20mL) were converted to the title compound in the same way as that described in Example 8, Step 5. The crude residue was chromatographed on silica gel, eluting with CH₂Cl₂:MeOH (92.5:7.5→85:15), to afford the piperazine (136mg, 61%) as a pale yellow foam. The hydrogen oxalate salt was prepared. mp. 65°C (dec.). C₃₂H₃₃N₆O₇. 1.5(C₂H₂O₄). 0.3(H₂O) requires: C, 61.90; H, 5.73; N, 12.38%. Found: C, 61.90; H, 5.89; N, 12.46%. ¹H NMR (360MHz, d₆-DMSO+TFA) δ 2.00-2.08 (2H, m), 2.50-3.76 (12H, m), 3.89-3.97 (1H, m), 4.02-4.11 (1H, m), 4.57-4.65 (3H, m), 7.27-7.46 (9H, m), 7.51-7.61 (3H, m), 7.95 (1H, s), 9.81 (2H, s), 11.33 (1H, br s). MS (ES⁺) (539, M+1).

25

30

EXAMPLE 10

1-[3-(5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl)propyl]-4-[2-(imidazol-1-yl)-1-phenylethyl]piperazine. 2.5 Hydrogen Oxalate

5

Intermediate 4: 1-(3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl)-4-[2-hydroxy-1-phenylethyl]piperazine

10 a) Methyl 2-phenyl-2-[1-(3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl)piperazin-4-yl]ethyl acetate

In the same way as that described in Example 1, Step 2, using Intermediate 2 (200mg, 0.64mmol), methyl α -bromophenyl acetate (112 μ L, 0.71mmol), K₂CO₃ (98mg, 0.71mmol) and DMF (5mL). The crude residue was chromatographed on silica gel, eluting with CH₂Cl₂:MeOH (93:7), to afford the ester (205mg, 70%) as a cream foam. ¹H NMR (250MHz, CDCl₃) δ 1.92-2.02 (2H, m), 2.42-2.70 (10H, m), 2.78 (2H, t, J=7.4Hz), 3.67 (3H, s), 4.00 (1H, s), 7.10-7.18 (2H, m), 7.27-7.41 (5H, m), 7.48 (1H, d, J=8.5Hz), 7.54 (1H, d, J=2.0Hz), 8.47 (2H, s), 9.05 (1H, br s).

20 b) 1-(3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl)-4-[2-hydroxy-1-phenylethyl]piperazine

In the same way as that described in Example 5, Step 3, using methyl 2-phenyl-2-[1-(3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl)piperazin-4-yl]ethyl acetate (620mg, 1.35mmol), LiAlH₄ (1.62mL of a 1.0M solution in ether, 1.62mmol), THF (20mL) and Na₂SO₄ solution (sat., 5mL). The alcohol (485mg, 84%) was isolated as a colourless foam. ¹H NMR (360MHz, CDCl₃) δ 1.81-1.90 (2H, m), 2.32-2.70 (10H, m), 2.74 (2H, t, J=7.6Hz), 3.64-3.70 (2H, m), 3.96 (1H, t, J=11Hz), 7.11-7.19 (4H, m), 7.28-7.35 (3H, m), 7.45 (1H, d, J=8.6Hz), 7.52 (1H, d, J=2.0Hz), 8.35 (1H, br s), 8.44 (2H, s). MS (431, M+1).

30

1-[3-(5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl)propyl]-4-[2-(imidazol-1-yl)-1-phenylethyl]piperazine. 2.5 Hydrogen Oxalate

In the same way as that described in Example 6, using 1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)-4-[2-hydroxy-1-phenylethyl]piperazine (100mg, 0.23mmol), triethylamine (65μL, 0.47mmol), methanesulphonyl chloride (36μL, 0.47mmol) and THF (5mL). The crude mesylate was then reacted with imidazole (317mg, 4.7mmol) in the same way as that described in Example 6. The title compound (13mg, 12%) was isolated as a pale yellow gum. The hydrogen oxalate salt was prepared, mp. 130°C (dec.). $C_{28}H_{32}N_8 \cdot 2.5(C_2H_2O_4) \cdot 1.2(H_2O)$ requires: C, 54.50; H, 5.46; N, 15.41%. Found: C, 54.36; H, 5.48; N, 15.59%. 1H NMR (250MHz, d_6 -DMSO) δ 1.95-2.12 (2H, m), 2.45-3.50 (14H, m), 5.65-5.70 (1H, m), 7.12 (1H, s), 7.33-7.51 (9H, m), 7.79 (1H, d, $J=1.9Hz$), 8.27 (1H, s), 9.02 (2H, s), 11.19 (1H, br s). MS (ES^+) (481, $M+1$).

EXAMPLE 11

1-[3-(5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl)propyl]-4-[1-phenyl-2-(pyrrolidin-1-yl)ethyl]piperazine. 2.4 Hydrogen Oxalate

In the same way as that described in Example 6, using 1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-4-[2-hydroxy-1-phenylethyl]piperazine (167mg, 0.39mmol), triethylamine (108μL, 0.78mmol), methanesulphonyl chloride (60μL, 0.78mmol) and THF (8mL). The crude mesylate was then reacted with pyrrolidine (0.65mL, 7.8mmol) in the same way as that described in Example 6. The title amine (39mg, 21%) was isolated as pale yellow foam. The hydrogen oxalate salt was prepared. mp. 135°C (dec.). $C_{29}H_{37}N_7 \cdot 2.4(C_2H_2O_4) \cdot H_2O$ requires: C, 56.56; H, 6.15; N, 13.66%. Found: C, 56.65; H, 6.35; N, 13.37%. 1H NMR (360MHz, d_6 -DMSO) δ 1.66-1.86 (4H, m), 1.97-2.07 (2H, m), 2.43-3.33 (18H, m), 4.43-4.51 (1H, m), 7.29-7.34 (2H, m), 7.42-7.52 (6H, m), 7.79 (1H, s), 9.01 (2H, s), 11.17 (1H, br s). MS (ES^+) (484, $M+1$).

EXAMPLE 12

1-[3-(5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl)propyl]-4-[2-(oxazolidin-2-on-3-yl)-
5 1-phenylethyl]piperazine. 1.25 Hydrogen Oxalate

Step 1: 1-[3-(5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl)propyl]-4-[2-amino-1-phenylethyl]piperazine

In the same way as that described in Example 7, Step 1 using 1-[3-
10 (5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-4-[2-hydroxy-1-phenylethyl]piperazine (330mg, 0.77mmol), triethylamine (214μL, 1.53mmol), methanesulphonyl chloride (118μL, 1.53mmol) and THF (15mL). The crude mesylate was then reacted with ammonia (7.7mL of a 2.0M solution in MeOH, 15.3mmol) in the same way as that described in
15 Example 7, Step 1. The amine (185mg, 56%) was isolated as a pale yellow foam. ¹H NMR (250MHz, CDCl₃) δ 1.88-2.00 (2H, m), 2.38-2.76 (12H, m), 2.79 (2H, t, J=7.5Hz), 4.11 (1H, dd, J=10.4 and 3.6Hz), 7.13-7.18 (2H, m), 7.22-7.39 (5H, m), 7.47 (1H, d, J=8.6Hz), 7.59 (1H, s), 8.34 (1H, br s), 8.46 (2H, s). MS (430, M+1).

20

Step 2: 1-[3-(5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl)propyl]-4-[2-(2-chloroethylcarbamoyl)-1-phenylethyl]piperazine

In the same way as that described in Example 7, Step 2, using 1-[3-
(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-4-[2-amino-1-
25 phenylethyl]piperazine (138mg, 0.32mmol), 2-chloroethyl chloroformate (35μL, 0.34mmol), NaOH solution (142μL of a 10% (w/v) solution, 0.35mmol), dioxane (3mL) and water (1.5mL). The carbamate (106mg, 62%) was isolated as a colourless foam. ¹H NMR (360MHz, CDCl₃) δ 1.88-1.99 (2H, m), 2.37-2.68 (12H, m), 2.77-2.83 (2H, m), 3.50-3.77 (2H, m),
30 4.20-4.33 (2H, m), 4.61-4.71 (1H, m), 5.77-5.85 (1H, m), 7.13-7.16 (2H, m),

7.21-7.35 (5H, m), 7.46 (1H, d, J=8.5Hz), 7.56 (1H, d, J=2.0Hz), 8.37 (1H, br s), 8.46 (2H, s). MS(ES⁺) (536/538, M+1).

5 Step 3: 1-[3-(5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl)propyl]-4-[2-(oxazolidin-2-on-3-yl)-1-phenylethyl]piperazine. 1.25 Hydrogen Oxalate

In the same way as that described in Example 7, Step 3, using 1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-4-[2-(2-chloroethylcarbamoyl)-1-phenylethyl]piperazine (106mg, 0.2mmol), sodium hydride (10mg of a 60% dispersion in mineral oil, 0.25mmol) and DMF (4mL). The crude
10 residue was chromatographed on silica gel, eluting with CH₂Cl₂:MeOH:NH₃ (95:5:0.5). The title compound (87mg, 87%) was isolated as a colourless foam. The hydrogen oxalate salt was prepared. mp. 136°C (dec.). C₂₈H₃₃N₇O₂. 1.25(C₂H₂O₄). 0.25(H₂O) requires: C, 59.41; H, 5.88; N, 15.90%. Found: C, 59.32; H, 5.96; N, 15.78%. ¹H NMR
15 (360MHz, d₆-DMSO) δ 1.95-2.07 (2H, m), 2.49-3.14 (14H, m), 3.26-3.34 (1H, m), 3.56-3.65 (1H, m), 4.20-4.33 (2H, m), 4.98-5.05 (1H, m), 7.30-7.41 (7H, m), 7.49 (1H, d, J=8.5Hz), 7.80 (1H, d, J=2.0Hz), 9.01 (2H, s), 11.16 (1H, br s). MS (ES⁺) (500, M+1).

20

EXAMPLE 13

1-[3-(5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl)propyl]-4-[2-(oxazol-2-on-3-yl)-1-phenylethyl]piperazine. 1.5 Hydrogen Oxalate

To a solution of 1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-4-[2-
25 hydroxy-1-phenylethyl]piperazine (100mg, 0.23mmol) in THF (5mL) at 0°C, was added triethylamine (49μL, 0.35mmol) followed by methanesulphonyl chloride (27μL, 0.35mmol). The cooling bath was removed and the mixture stirred at room temperature for 35min. The solid was removed by filtration and the filtrate partially evaporated
30 (approx. 3mL remaining) and diluted with DMF (5mL). This filtrate was then added to a solution of oxazol-2-one sodium salt in DMF (2mL). (The

sodium salt was prepared by adding sodium hydride (18.6mg of a 60% dispersion in mineral oil, 0.47mmol) to a solution of oxazol-2-one (40mg, 0.47mmol) in DMF (2mL) and stirring for 1h at room temperature). The mixture was stirred at room temperature for 90min then the solvent was removed *in vacuo* and the residue partitioned between CH₂Cl₂ (2x25mL) and water (20mL). The combined organic layers were dried (Na₂SO₄) and evaporated. The residue was chromatographed on silica gel, eluting with CH₂Cl₂:MeOH:NH₃ (90:10:0→90:10:1). The title compound (30mg, 26%) was isolated as a cream foam. The hydrogen oxalate salt was prepared, mp. 125°C (dec.). C₂₈H₃₁N₇O₂. 1.5(C₂H₂O₄). 0.5(H₂O) requires: C, 58.03; H, 5.50; N, 15.28%. Found: C, 58.23; H, 5.73; N, 15.38%. ¹H NMR (360MHz, d₆-DMSO) δ 1.93-2.07 (2H, m), 2.47-3.30 (14H, m), 5.15-5.21 (1H, m), 7.21 (1H, d, J=2.0Hz), 7.27-7.40 (8H, m), 7.49 (1H, d, J=8.6Hz), 7.79 (1H, d, J=1.9Hz), 9.01 (2H, s), 11.16 (1H, br s). MS (ES⁺) (498, M+1).

15

EXAMPLE 14

1-[3-(5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl)propyl]-4-[3-(imidazol-1-yl)-1-phenylpropyl]piperazine. 2.5 Hydrogen Oxalate

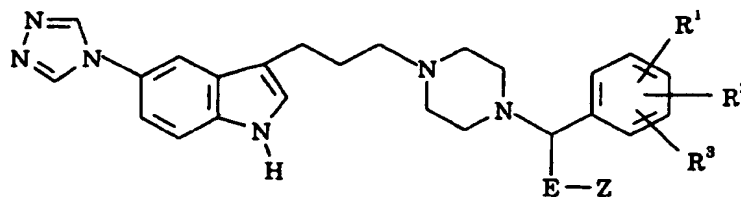
20 In the same way as that described in Example 6, using 1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-4-[3-hydroxy-1-phenylpropyl]piperazine (200mg, 0.45mmol), triethylamine (125μL, 0.9mmol), methanesulphonyl chloride (70μL, 0.9mmol) and THF (10mL). The crude mesylate was then reacted with imidazole (613mg, 9.0mmol) in the same way as that described in Example 6, to give the title compound (57mg, 26%) as a pale yellow foam. The hydrogen oxalate salt was prepared. mp. 90°C (dec.). C₂₉H₃₄N₈. 2.5(C₂H₂O₄). 2.5(H₂O) requires: C, 53.40; H, 5.80; N, 14.65%. Found: C, 53.34; H, 5.86; N, 14.50%. ¹H NMR (360MHz, d₆-DMSO) δ 1.98-2.09 (2H, m), 2.26-2.43 (4H, m), 2.57-2.81 (6H, m), 2.98-3.21 (6H, m), 5.46-5.55 (1H, m), 7.11 (1H, s), 7.27-7.42 (7H, m),

30

7.46 (1H, s), 7.51 (1H, d, J=8.6Hz), 7.81 (1H, s), 8.20 (1H, s), 9.02 (2H, s),
11.18 (1H, br s). MS (ES⁺) (495, M+1).

CLAIMS:

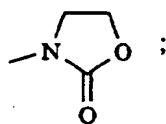
1. A compound of formula I, or a salt or prodrug thereof:



(I)

wherein

R¹ represents hydrogen, halogen, trifluoromethyl, C₁₋₆ alkoxy or a group of formula (a):

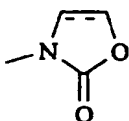


(a)

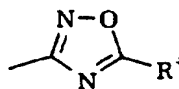
R² and R³ independently represent hydrogen, halogen, trifluoromethyl or C₁₋₆ alkoxy;

E represents a straight or branched alkylene chain containing from 1 to 4 carbon atoms; and

Z represents hydroxy, C₁₋₆ alkoxy, aryl(C₁₋₆)alkoxy, an imidazolyl or pyrrolidinyl group, or a group of formula (Za) or (Zb):



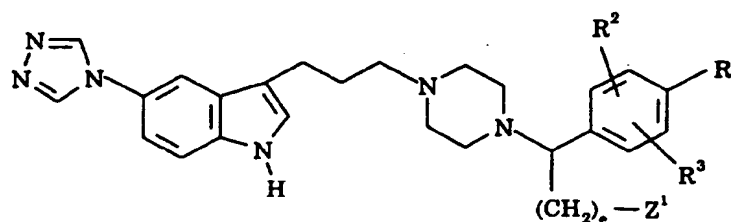
(Za)



(Zb)

in which the broken line represents an optional chemical bond; and
 R^4 represents C_{1-6} alkyl.

- 5 2. A compound as claimed in claim 1 represented by formula II,
 and salts and prodrugs thereof:



(II)

- 10 wherein R^1 , R^2 and R^3 are as defined in claim 1;
 e is 1 or 2; and
 Z^1 represents hydroxy, methoxy, benzyloxy, imidazol-1-yl,
 pyrrolidin-1-yl, oxazol-2-on-3-yl, oxazolidin-2-on-3-yl or 5-methyl-1,2,4-
 oxadiazol-3-yl.
- 15 3. A compound as claimed in claim 2 wherein R^1 represents
 hydrogen, fluoro or trifluoromethyl.
4. A compound as claimed in claim 2 or claim 3 wherein R^2 is
 20 hydrogen and R^3 is other than hydrogen.
5. A compound as claimed in claim 2 or claim 3 wherein R^2 and
 R^3 are both hydrogen.
- 25 6. A compound selected from:

- 1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[2-(oxazol-2-on-3-yl)-1-phenylethyl]piperazine;
- 1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[2-(oxazolidin-2-on-3-yl)-1-phenylethyl]piperazine;
- 5 1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[1-(4-fluorophenyl)-2-(oxazolidin-2-on-3-yl)ethyl]piperazine;
- 1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-(3-hydroxy-1-phenylpropyl)piperazine;
- 10 1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[2-(imidazol-1-yl)-1-phenylethyl]piperazine;
- 1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[1-(4-fluorophenyl)-2-hydroxyethyl]piperazine;
- 1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[1-(4-fluorophenyl)-2-methoxyethyl]piperazine;
- 15 1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[3-(5-methyl-1,2,4-oxadiazol-3-yl)-1-phenylpropyl]piperazine;
- 1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[2-benzyloxy-1-(4-fluorophenyl)ethyl]piperazine;
- 1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[1-(4-fluorophenyl)-3-
- 20 methoxypropyl]piperazine;
- 1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[1-(4-fluorophenyl)-2-(imidazol-1-yl)ethyl]piperazine;
- 1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[1-phenyl-2-(pyrrolidin-1-yl)ethyl]piperazine;
- 25 1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[1-(4-fluorophenyl)-3-hydroxypropyl]piperazine;
- 1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[3-(imidazol-1-yl)-1-phenylpropyl]piperazine;
- and salts and prodrugs thereof.

7. A pharmaceutical composition comprising a compound of formula I as defined in claim 1 or a pharmaceutically acceptable salt thereof or a prodrug thereof in association with a pharmaceutically acceptable carrier.

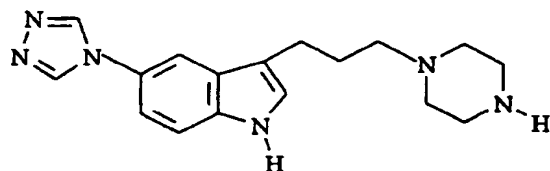
5

8. A compound as claimed in any one of claims 1 to 6 for use in therapy.

9. The use of a compound as claimed in any one of claims 1 to 6 for the manufacture of a medicament for the treatment and/or prevention of clinical conditions for which an agonist of 5-HT_{1D} receptors selective for the 5-HT_{1D α} subtype thereof is indicated.

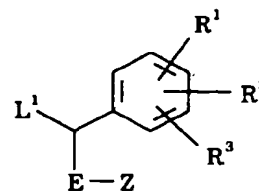
10. A process for the preparation of a compound as claimed in any one of claims 1 to 6, which comprises:

(A) reacting the compound of formula III with a compound of formula IV:



(III)

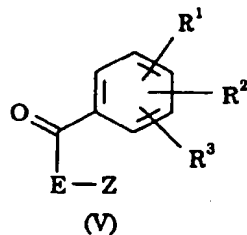
20



(IV)

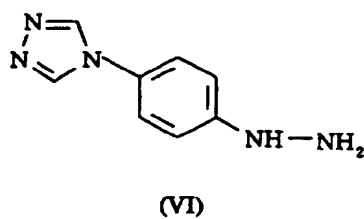
wherein R¹, R², R³, E and Z are as defined in claim 1, and L¹ represents a suitable leaving group; or

(B) reacting the compound of formula III as defined above with a compound of formula V:



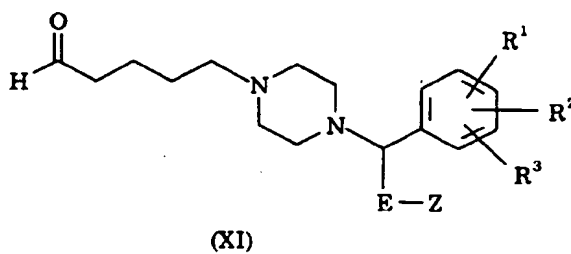
wherein R^1 , R^2 , R^3 , E and Z are as defined in claim 1; in the presence of a
 5 reducing agent; or

(C) reacting the compound of formula VI:



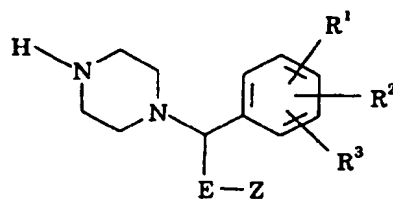
10

with a compound of formula XI, or a carbonyl-protected form thereof:



15 wherein R^1 , R^2 , R^3 , E and Z are as defined in claim 1; or

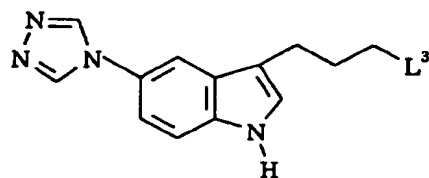
(D) reacting a compound of formula XIII:



(XIII)

wherein R^1 , R^2 , R^3 , E and Z are as defined in claim 1; with a compound of formula XIV:

5

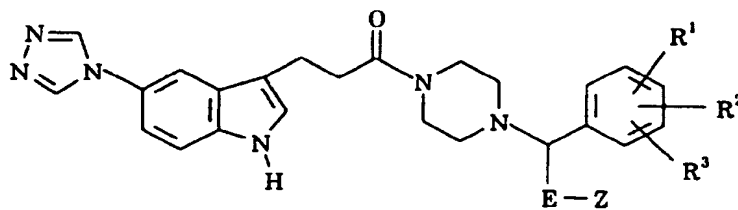


(XIV)

wherein L^3 represents a suitable leaving group; or

10

(E) reducing a compound of formula XVII:

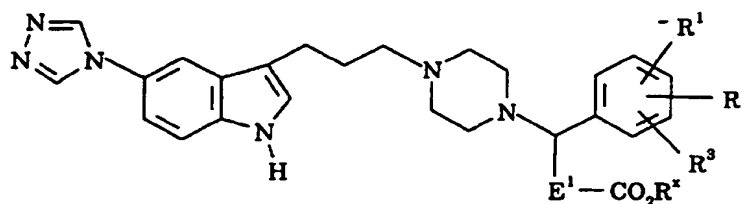


(XVII)

wherein R^1 , R^2 , R^3 , E and Z are as defined in claim 1; or

15

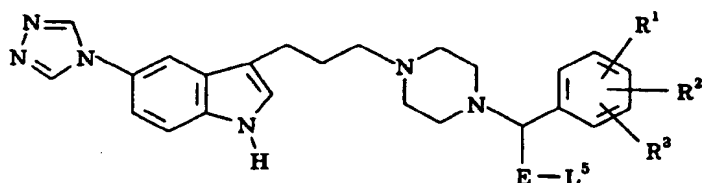
(F) reducing a compound of formula XIX:



(XIX)

wherein E^1 represents a chemical bond or a straight or branched alkylene chain containing from 1 to 3 carbon atoms, R^x represents C_{1-6} alkyl, and
 5 R^1 , R^2 and R^3 are as defined in claim 1; or

(G) reacting a compound of formula XX with a compound of formula XXI:



(XX)



(XXI)

wherein Z^2 represents imidazol-1-yl, pyrrolidin-1-yl, oxazol-2-on-3-yl or oxazolidin-2-on-3-yl, L^5 represents a suitable leaving group, and R^1 , R^2 , R^3 and E are as defined in claim 1; and

(H) subsequently, where appropriate, converting a compound of formula I initially obtained into a further compound of formula I by standard methods.

11. A method for the treatment and/or prevention of clinical conditions for which an agonist of 5-HT_{1D} receptors selective for the 5-HT_{1D α} subtype thereof is indicated, which method comprises

administering to a patient in need of such treatment an effective amount of a compound of formula I as defined in claim 1 or a pharmaceutically acceptable salt thereof or a prodrug thereof.

INTERNATIONAL SEARCH REPORT

Intern. Application No.
PCT/GB 96/02682

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D403/14 C07D413/14 A61K31/495

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 94 02477 A (MERCK SHARP & DOHME LTD.) 3 February 1994 cited in the application see claims	1-11
P,A	WO 95 32196 A (MERCK SHARP & DOHME LTD.) 30 November 1995 see claims	1-11
P,A	WO 96 16056 A (MERCK SHARP & DOHME LTD.) 30 May 1996 see claims	1-11

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *A* document member of the same patent family

Date of the actual completion of the international search

17 January 1997

Date of mailing of the international search report

24. 01. 97

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Chouly, J

INTERNATIONAL SEARCH REPORT

International application No.

.../GB 96/02682

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 11 is directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/GB 96/02682

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9402477	03-02-94	AU-B- 672802	17-10-96
		AU-A- 4578593	14-02-94
		CA-A- 2138649	03-02-94
		EP-A- 0651749	10-05-95
		JP-T- 7509452	19-10-95
		US-A- 5567726	22-10-96

WO-A-9532196	30-11-95	AU-A- 2529695	18-12-95

WO-A-9616056	30-05-96	AU-A- 3875095	17-06-96
